

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
26 February 2004 (26.02.2004)

PCT

(10) International Publication Number
WO 2004/016578 A2

(51) International Patent Classification⁷: **C07C 217/10**, 311/39, 213/00, 303/40, C07D 215/26, 213/65, 265/36, 277/68

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(21) International Application Number:

PCT/EP2003/008264

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(22) International Filing Date: 24 July 2003 (24.07.2003)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

0217225.2 25 July 2002 (25.07.2002) GB

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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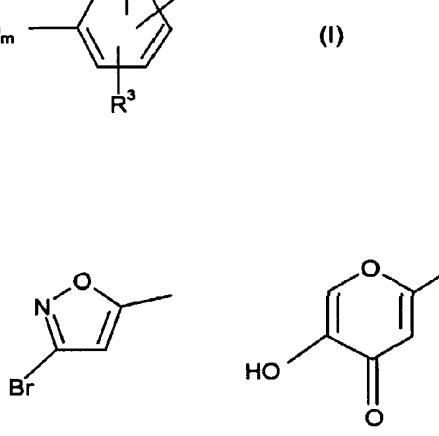
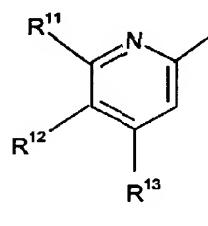
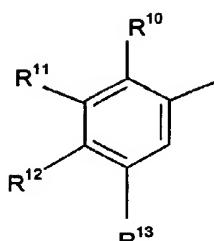
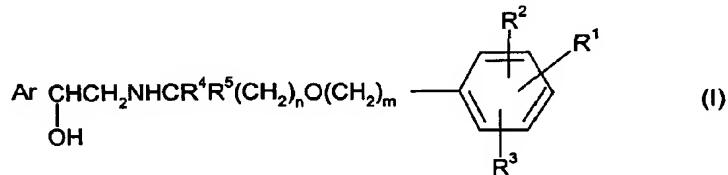
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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[Continued on next page]

(54) Title: MEDICINAL COMPOUNDS



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(57) **Abstract:** The present invention concerns compounds of formula (I) and salts, solvates, and physiologically functional derivatives thereof, wherein: R¹ is hydrogen or -XSO₂NR⁶R⁷; R² and R³ are independently selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo, phenyl and C₁₋₆ haloalkyl and Ar is a group selected from and. Processes for preparing said compounds and pharmaceutical formulations containing them are also described. Compounds of formula (I) are useful in the treatment of respiratory diseases



Published:

- without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

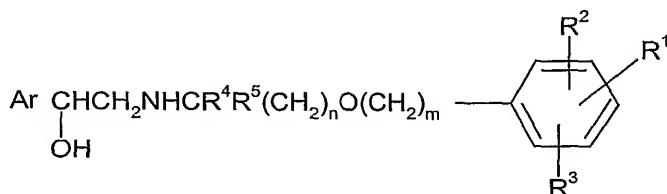
Medicinal Compounds

The present invention is concerned with phenethanolamine derivatives, processes for their preparation, compositions containing them and their use in medicine, particularly in
5 the prophylaxis and treatment of respiratory diseases.

Certain phenethanolamine compounds are known in the art as having selective stimulant action at β_2 -adrenoreceptors and therefore having utility in the treatment of bronchial asthma and related disorders. Thus GB 2 140 800 describes phenethanolamine
10 compounds including 4-hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-naphthalenecarboxylate (salmeterol xinafoate) which is now used clinically in the treatment of such medical conditions.

Although salmeterol and the other commercially available β_2 -adrenoreceptor agonists are effective bronchodilators, the maximum duration of action is 12 hours, hence twice daily dosing is often required. There is therefore a clinical need for compounds having potent and selective stimulant action at β_2 -adrenoreceptors and having an advantageous profile of action.

20 According to the present invention, there is provided a compound of formula (I)



(I)

or a salt, solvate, or physiologically functional derivative thereof, wherein:

25

n is an integer of from 2 to 8;

m is an integer of from 3 to 11, preferably from 3 to 7, with the proviso that the sum of n + m is from 5 to 19, preferably 5 to 12;

• R¹ is hydrogen or -XSO₂NR⁶R⁷;

wherein X is -(CH₂)_p- or C₂₋₆ alkenylene;

5 p is an integer from 0 to 6, preferably 0 to 4;

R⁶ and R⁷ are independently selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, CONR⁸R⁹, phenyl and phenyl(C₁₋₄alkyl)-,

10 or R⁶ and R⁷, together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered nitrogen – containing ring;

and R⁶ and R⁷ are each independently optionally substituted by 1 or 2 groups independently selected from halo, C₁₋₆alkyl, C₁₋₆alkoxy, hydroxy-substituted C₁₋₆alkoxy,

15 C₁₋₆haloalkyl, CO₂R⁸, SO₂R⁸R⁹, -CONR⁸R⁹, -NR⁸C(O)R⁹ or a 5-, 6- or 7- membered heterocyclic ring;

R⁸ and R⁹ are independently selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, phenyl and phenyl(C₁₋₆alkyl)-;

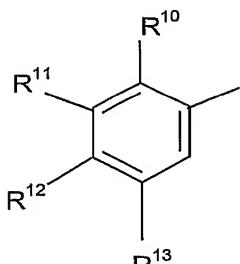
20 R² and R³ are independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, halo, phenyl and C₁₋₆haloalkyl;

25 R⁴ and R⁵ are independently selected from hydrogen and C₁₋₄ alkyl with the proviso that the total number of carbon atoms in R⁴ and R⁵ is not more than 4,

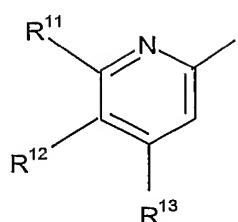
and

Ar is a group selected from

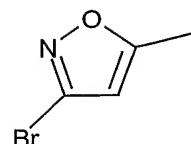
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(a)

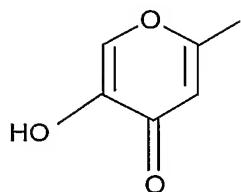


(b)



(c)

and



(d)

wherein R¹¹ represents hydrogen, halogen, -(CH₂)_qOR¹⁴, -NR¹⁴C(O)R¹⁵, -NR¹⁴SO₂R¹⁵, -SO₂NR¹⁴R¹⁵, -NR¹⁴R¹⁵, -OC(O)R¹⁶ or OC(O)NR¹⁴R¹⁵,

5 and R¹⁰ represents hydrogen, halogen or C₁₋₄alkyl;

or R¹¹ represents -NHR¹⁷ and R¹⁰ and -NHR¹⁷ together form a 5- or 6- membered heterocyclic ring;

10 R¹² represents hydrogen, halogen, -OR¹⁴ or -NR¹⁴R¹⁵;

R¹³ represents hydrogen, halogen, haloC₁₋₄alkyl, -OR¹⁴, -NR¹⁴R¹⁵ OC(O)R¹⁶ or OC(O)NR¹⁴R¹⁵;

15 R¹⁴ and R¹⁵ each independently represents hydrogen or C₁₋₄ alkyl, or in the groups -NR¹⁴R¹⁵, -SO₂NR¹⁴R¹⁵ and -OC(O)NR¹⁴R¹⁵, R¹⁴ and R¹⁵ independently represent hydrogen or C₁₋₄ alkyl or together with the nitrogen atom to which they are attached form a 5-, 6- or 7- membered nitrogen-containing ring,

R^{16} represents an aryl (eg phenyl or naphthyl) group which may be unsubstituted or substituted by one or more substituents selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy or halo C_{1-4} alkyl; and

5

q is zero or an integer from 1 to 4;

provided that when R^1 is hydrogen

Ar is not a group (a) wherein;

- 10 R^{11} is $-(CH_2)_qOR^{14}$, q is zero or 1 and R^{12} is OR^{14} ,
or R^{11} is $-(CH_2)_qOR^{14}$, q is zero and R^{13} is OR^{14} ,
or R^{11} is $-NR^{14}SO_2R^{15}$ or $NR^{14}COR^{15}$ and R^{12} is OR^{14} ,
or R^{11} and R^{13} both represent halogen and R^{12} is $NR^{14}R^{15}$;
 Ar is not a group (b) wherein R^{11} is $-(CH_2)_qOR^{14}$ and R^{12} is OR^{14} ;
- 15 Ar is not a group (c),
and when R^1 is $XSO_2NR^6R^7$, Ar is not a group (a) wherein
 R^{11} is $(CH_2)_qOR^{14}$ or $NR^{14}COR^{15}$, and R^{12} is OR^{14} .

In a particular embodiment of this invention, in the group Ar , R^{11} represents halogen,

- 20 $-(CH_2)_qOR^{14}$, $-NR^{14}C(O)R^{15}$, $-NR^{14}SO_2R^{15}$, $-SO_2NR^{14}R^{15}$, $-NR^{14}R^{15}$, $-OC(O)R^{16}$ or
 $OC(O)NR^{14}R^{15}$,

and R^{10} represents hydrogen,

- 25 or R^{11} represents $-NHR^{17}$ and R^{10} and $-NHR^{17}$ together form a 5- or 6- membered heterocyclic ring;

and

- 30 R^{13} represents hydrogen, halogen, halo C_{1-4} alkyl, $-OR^{14}$, or $-NR^{14}R^{15}$;

and all other substituents are as defined above.

- 35 In the compounds of formula (I), the group R^1 is preferably attached to the meta-position relative to the $-O-(CH_2)_m$ link.

R^1 preferably represents $\text{SO}_2\text{NR}^6\text{R}^7$ wherein R^6 and R^7 are independently selected from hydrogen and C_{1-6} -alkyl. More preferably R^1 is SO_2NH_2 .

- 5 R^4 and R^5 are preferably independently selected from hydrogen and methyl, more preferably R^4 and R^5 are both hydrogen.

In the compounds of formula (I) R^2 and R^3 preferably each represent hydrogen.

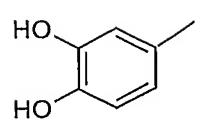
- 10 The integer n is suitably 4, 5 or 6 and m is suitably 3, 4, 5 or 6. Preferably n is 5 or 6 and m is 3 or 4 such that $m + n$ is 8, 9 or 10, preferably 9.

In the compounds of formula (I) the group Ar is preferably selected from groups (a) and (b) above. In said groups (a) and (b), when R^{11} represents halogen this is preferably chlorine or fluorine, especially fluorine. R^{14} and R^{15} preferably each independently represent hydrogen or methyl. R^{16} preferably represents substituted phenyl. The integer q preferably represents zero or 1. Thus for example $-(\text{CH}_2)_q\text{OR}^{14}$ preferably represents OH or $-\text{CH}_2\text{OH}$;

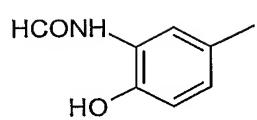
- 15 $\text{NR}^{14}\text{C(O)R}^{15}$ preferably represents $-\text{NHC(O)H}$;
 20 $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$ preferably represents $-\text{SO}_2\text{NH}_2$ or SO_2NHCH_3 ;
 $\text{NR}^{14}\text{R}^{15}$ preferably represents $-\text{NH}_2$;
 $-\text{OC(O)R}^{16}$ preferably represents substituted benzyloxy eg. $\text{OC(O)-C}_6\text{H}_4-(p\text{-CH}_3)$; and
 $-\text{OC(O)N R}^{14}\text{R}^{15}$ preferably represents $\text{OC(O)N(CH}_3)_2$.

- 25 When R^{11} represents NHR^{17} and together with R^{10} forms a 5- or 6-membered heterocyclic ring $-\text{NHR}^{17}-\text{R}^{10}-$ preferably represents a group:
 $-\text{NH-CO-R}^{18}$ where R^{18} is an alkylene, and alkenylene or alkenyloxy group,
 $-\text{NH-SO}_2\text{R}^{19}$ where R^{19} is an alkenyloxy group,
 $-\text{NH-R}^{20}(\text{COOR}^{21})$ where R^{19} is an alkylene or alkenylene group and R^{20} is C_{1-4} alkyl, or
 30 $-\text{NH-CO-CH-}$ or NH-CO-S ,
 wherein said alkylene, and alkenylene groups and moieties contain 1 or 2 carbon atoms.

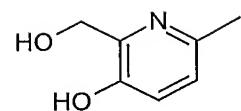
Particularly preferred groups (a) and (b) may be selected from the following groups (i) to (xx):



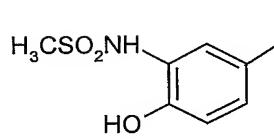
(i)



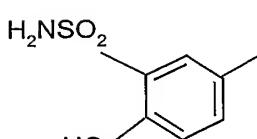
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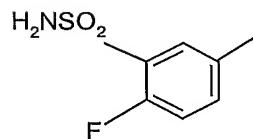
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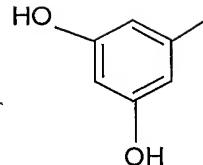
(iv)



(v)

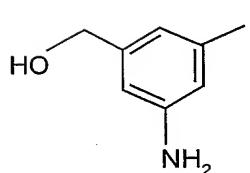


(vi)



(vii)

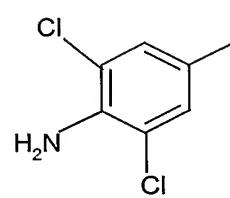
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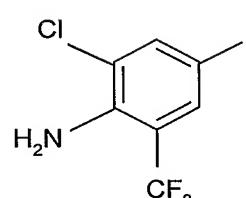
(viii)



(ix)

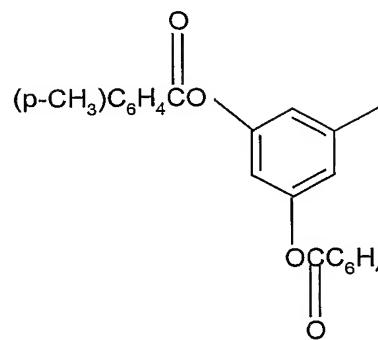


(x)

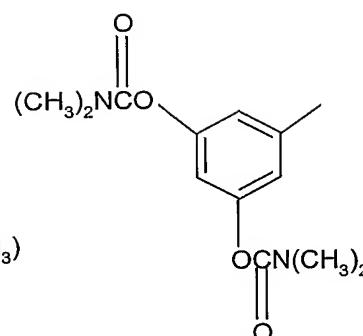


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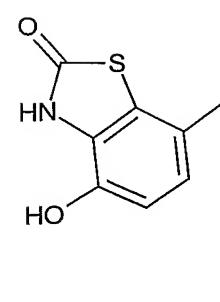
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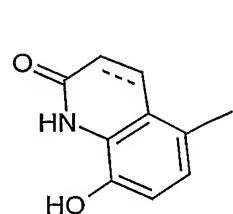
(xii)



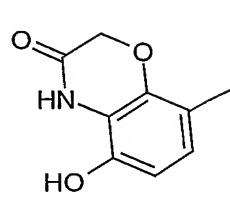
(xiii)



(xiv)



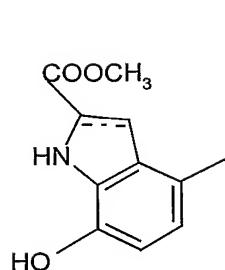
(xv)



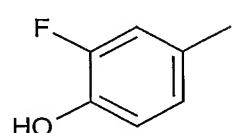
(xvi)



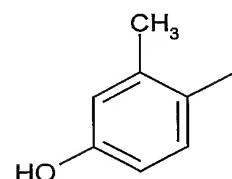
(xvii)



(xviii)



(xix)



(xx)

5

wherein the dotted line in (xv) and (xviii) denotes an optional double bond.

It will be appreciated that when R¹ represents hydrogen, Ar is not a group having the
5 structure (i), (iii), (iv), (vii) or (x). Furthermore, when R¹ represents a group -XSO₂NR⁶R⁷,
Ar is not a group having the structure (ii).

Thus, when R¹ is hydrogen, Ar is preferably selected from a group of structure (ii), (v), (vi),
(viii), (ix), (xi), (xii), (xiii), (xiv), (xv), (xvi), (xvii) and (xviii).

10

Most preferably when R¹ is hydrogen Ar is selected from a group of structure (xiv), (xv),
(xvi) and (xvii).

When R¹ is XSO₂NR⁶R⁷, Ar is preferably selected from a group of structure (iii), (iv), (xiv),
15 (xv), (xvi) and (xix).

It is to be understood that the present invention covers all combinations of particular and
preferred groups described hereinabove.

20 Preferred compounds of the invention include:

8-Hydroxy-5-((1*R*)-1-hydroxy-2-{[6-(4-phenylbutoxy)hexyl]amino}ethyl)quinolin-2(1*H*)-one;
3-{4-[(6-[(2*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-
yl)ethyl]amino}hexyl]oxy]butyl}benzenesulfonamide;
25 5-Hydroxy-8-(1-hydroxy-2-{[6-(4-phenylbutoxy)hexyl]amino}ethyl)-2*H*-1,4-benzoxazin-
3(4*H*)-one;
3-{4-[(6-[(2-hydroxy-2-(5-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-8-
yl)ethyl]amino}hexyl]oxy]butyl}benzenesulfonamide;
4-Hydroxy-7-((1*R*)-1-hydroxy-2-{[6-(4-phenylbutoxy)hexyl]amino}ethyl)-1,3-benzothiazol-
30 2(3*H*)-one;
4-Hydroxy-7-(1-hydroxy-2-{[6-(4-phenylbutoxy)hexyl]amino}ethyl)-1,3-benzothiazol-2(3*H*)-
one;
3-{4-[(6-[(2*R*)-2-(3-Fluoro-4-hydroxyphenyl)-2-
hydroxyethyl]amino}hexyl]oxy]butyl}benzenesulfonamide;

3-(4-[{6-({2-Hydroxy-2-[5-hydroxy-6-(hydroxymethyl)pyridin-2-yl]ethyl}amino)hexyl]oxy]butyl)benzenesulfonamide;
3-[4-{[6-[(2R)-2-Hydroxy-2-{4-hydroxy-3-
[(methylsulfonyl)amino]phenyl}ethyl]amino]hexyl]oxy]butyl]benzenesulfonamide;

- 5 3-{3-[(7-[(2R)-2-(3-Fluoro-4-hydroxyphenyl)-2-
hydroxyethyl]amino)heptyl]oxy]propyl}benzenesulfonamide;
3-(3-[(7-({2-Hydroxy-2-[5-hydroxy-6-(hydroxymethyl)pyridin-2-
yl]ethyl}amino)heptyl]oxy)propyl)benzenesulfonamide;
3-[3-{[7-[(2R)-2-Hydroxy-2-{4-hydroxy-3-
10 [(methylsulfonyl)amino]phenyl}ethyl]amino]heptyl]oxy]propyl]benzenesulfonamide;
3-{3-[(7-[(2R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-
yl)ethyl]amino)heptyl]oxy]propyl}benzenesulfonamide;
3-(3-[(7-((2R)-2-[3-(Formylamino)-4-hydroxyphenyl]-2-
hydroxyethyl]amino)heptyl]oxy)propyl)benzenesulfonamide;

15 and salts, solvates and physiologically functional derivatives thereof.

The compounds of formula (I) include an asymmetric centre, namely the carbon atom of the



20

group. The present invention includes both (S) and (R) enantiomers either in substantially pure form or admixed in any proportions. Preferably, the compounds of the invention are in the form of the (R) enantiomers.

25

Similarly, where R⁴ and R⁵ are different groups, the carbon atom to which they are attached is an asymmetric centre and the present invention includes both (S) and (R) enantiomers at this centre either in substantially pure form or admixed in any proportions.

30 Thus the compounds of formula (I) include all enantiomers and diastereoisomers as well as mixtures thereof in any proportions.

Salts and solvates of compounds of formula (I) which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable.

However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives.

5

By the term "physiologically functional derivative" is meant a chemical derivative of a compound of formula (I) having the same physiological function as the free compound of formula (I), for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

10

Suitable salts according to the invention include those formed with both organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, sulphamic, sulphanilic, succinic, oxalic, fumaric, maleic, malic, glutamic, aspartic, oxaloacetic, methanesulphonic, ethanesulphonic, arylsulphonic (for example p-toluenesulphonic, benzenesulphonic, naphthalenesulphonic or naphthalenedisulphonic), salicylic, glutaric, gluconic, tricarballylic, cinnamic, substituted cinnamic (for example, phenyl, methyl, methoxy or halo substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzeneacrylic (for example 1,4-benzenediacrylic) and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexyl amine and N-methyl-D-glucamine.

Pharmaceutically acceptable esters of the compounds of formula (I) may have a hydroxyl group converted to a C₁₋₆alkyl, aryl, aryl C₁₋₆alkyl, or amino acid ester.

30

As mentioned above, the compounds of formula (I) are selective β₂-adrenoreceptor agonists as demonstrated using functional or reporter gene readout from cell lines transfected with human beta-adrenoreceptors as described below. Compounds according to the present invention also have the potential to combine long duration of effect with rapid onset of action. Furthermore, certain compounds have shown an improved

therapeutic index in animal models relative to existing long-acting β_2 -agonist bronchodilators. As such, compounds of the invention may be suitable for once-daily administration.

5 Therefore, compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have use in the prophylaxis and treatment of clinical conditions for which a selective β_2 -adrenoreceptor agonist is indicated. Such conditions include diseases associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic 10 and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease.

Other conditions which may be treated include premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin 15 diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

Accordingly, the present invention provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor 20 agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. In particular, the present invention provides such a method for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), 25 respiratory tract infection or upper respiratory tract disease. In a further aspect the present invention provides such a method for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle 30 wasting disease.

In the alternative, there is also provided a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy, particularly, for use in the prophylaxis or treatment of a clinical condition in a 35 mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist is indicated.

In particular, there is provided a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect, there is provided a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2 -adrenoreceptor agonist is indicated, for example a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect, there is provided a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

The amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. The compounds of the invention may be administered by inhalation at a dose of from 0.0005mg to 10 mg, preferably 0.005mg to 0.5mg. The dose range for adult humans is generally from 0.0005 mg to 100mg per day and preferably 0.01 mg to 1mg per day.

While it is possible for the compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to be administered alone, it is preferable to present it as a pharmaceutical formulation.

Accordingly, the present invention further provides a pharmaceutical formulation comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or 5 excipient, and optionally one or more other therapeutic ingredients.

Hereinafter, the term "active ingredient" means a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

10 The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may
15 depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing
20 into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined
25 amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

30 A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the
35 powdered compound moistened with an inert liquid diluent. The tablets may optionally be

coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

- Formulations for parenteral administration include aqueous and non-aqueous sterile
5 injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes
which render the formulation isotonic with the blood of the intended recipient; and
aqueous and non-aqueous sterile suspensions which may include suspending agents and
thickening agents. The formulations may be presented in unit-dose or multi-dose
10 containers, for example sealed ampoules and vials, and may be stored in a freeze-dried
(lyophilised) condition requiring only the addition of the sterile liquid carrier, for example
saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions
and suspensions may be prepared from sterile powders, granules and tablets of the kind
previously described.
- 15 Dry powder compositions for topical delivery to the lung by inhalation may, for example,
be presented in capsules and cartridges of for example gelatine, or blisters of for example
laminated aluminium foil, for use in an inhaler or insufflator. Formulations generally
contain a powder mix for inhalation of the compound of the invention and a suitable
powder base (carrier substance) such as lactose or starch. Use of lactose is preferred.
20 Each capsule or cartridge may generally contain between 20 μ g-10mg of the compound of
formula (I) optionally in combination with another therapeutically active ingredient.
Alternatively, the compound of the invention may be presented without excipients.
Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the
case of multi-dose delivery, the formulation can be pre-metered (eg as in Diskus, see GB
25 2242134 or Diskhaler, see GB 2178965, 2129691 and 2169265) or metered in use (eg as
in Turbuhaler, see EP 69715). An example of a unit-dose device is Rotahaler (see GB
2064336). The Diskus inhalation device comprises an elongate strip formed from a base
sheet having a plurality of recesses spaced along its length and a lid sheet hermetically
but peelably sealed thereto to define a plurality of containers, each container having
30 therein an inhalable formulation containing a compound of formula (I) preferably combined
with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid
sheet and base sheet will preferably have leading end portions which are not sealed to
one another and at least one of the said leading end portions is constructed to be
attached to a winding means. Also, preferably the hermetic seal between the base and lid

sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

Spray compositions for topical delivery to the lung by inhalation may for example be

5 formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the compound of formula (I) optionally in combination with another therapeutically active ingredient and a suitable propellant such as a fluorocarbon
10 or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant.
15 The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants eg oleic acid or lecithin and cosolvents eg ethanol. Pressurised formulations will generally be retained in a canister (eg an aluminium canister) closed with a valve (eg a metering valve) and fitted into an actuator provided with a mouthpiece.

20 Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10 μm , preferably 2-5 μm . Particles having a size above 20 μm are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient as produced may be size reduced by conventional means eg by micronisation. The desired
25 fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline. When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as milled lactose, wherein not more than 85% of lactose particles will have a MMD of 60-90 μm and not less
30 than 15% will have a MMD of less than 15 μm .

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Solutions for inhalation by nebulisation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

5

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, 10 include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

Preferred unit dosage formulations are those containing an effective dose, as 15 hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral 20 administration may include flavouring agents.

The compounds and pharmaceutical formulations according to the invention may be used in combination with or include one or more other therapeutic agents, for example selected from anti-inflammatory agents, anticholinergic agents (particularly an M₁, M₂, M₁/M₂ or M₃ 25 receptor antagonist), other β₂-adrenoreceptor agonists, antiinfective agents (e.g. antibiotics, antivirals), or antihistamines. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with one or more other therapeutically active agents, for example selected from an anti-inflammatory agent 30 (for example a corticosteroid or an NSAID), an anticholinergic agent, another β₂-adrenoreceptor agonist, an antiinfective agent (e.g. an antibiotic or an antiviral), or an antihistamine. Preferred are combinations comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid, and/or an anticholinergic, and/or a PDE-4 inhibitor. 35 Preferred combinations are those comprising one or two other therapeutic agents.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, (e.g. as alkali metal or amine salts or as acid addition salts), or prodrugs, or as esters (e.g. lower alkyl esters), or as solvates (e.g. 5 hydrates) to optimise the activity and/or stability and/or physical characteristics (e.g. solubility) of the therapeutic ingredient. It will be clear also that where appropriate, the therapeutic ingredients may be used in optically pure form.

Suitable anti-inflammatory agents include corticosteroids and NSAIDs. Suitable 10 corticosteroids which may be used in combination with the compounds of the invention are those oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity. Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester, 15 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxy- androsta-1,4-diene-17 β -carbothioic acid S-(2-oxo-tetrahydro-furan-3S-yl) ester, beclomethasone esters (e.g. the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide, rofleponide, ciclesonide, butixocort propionate, RPR-106541, and ST-126. Preferred corticosteroids 20 include fluticasone propionate, 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester and 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester, more 25 preferably 6 α ,9 α -difluoro-17 α -[(2-furanylcarbonyl)oxy]-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester.

Suitable NSAIDs include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis, iNOS inhibitors, tryptase and 30 elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine antagonists) or inhibitors of cytokine synthesis. Suitable other β_2 -adrenoreceptor agonists include salmeterol (e.g. as the xinafoate), salbutamol (e.g. as the sulphate or the free base), formoterol (e.g. as the fumarate), fenoterol or terbutaline and salts thereof.

Of particular interest is use of the compound of formula (I) in combination with a phosphodiesterase 4 (PDE4) inhibitor or a mixed PDE3/PDE4 inhibitor. The PDE4-specific inhibitor useful in this aspect of the invention may be any compound that is known
5 to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the PDE family as well as PDE4. Generally it is preferred to use a PDE4 inhibitor which has an IC₅₀ ratio of about 0.1 or greater as regards the IC₅₀ for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC₅₀ for the form which binds rolipram with a
10 low affinity. For the purposes of this disclosure, the cAMP catalytic site which binds R and S rolipram with a low affinity is denominated the "low affinity" binding site (LPDE 4) and the other form of this catalytic site which binds rolipram with a high affinity is denominated the "high affinity" binding site (HPDE 4). This term "HPDE4" should not be confused with the term "hPDE4" which is used to denote human PDE4.

15

A method for determining IC₅₀ ratios is set out in US Patent 5,998,428, which is incorporated herein in full by reference as though set out herein. See also PCT application WO 00/57599 for another description of said assay.

20

The preferred PDE4 inhibitors of use in this invention will be those compounds which have a salutary therapeutic ratio, i.e., compounds which preferentially inhibit cAMP catalytic activity where the enzyme is in the form that binds rolipram with a low affinity, thereby reducing the side effects which apparently are linked to inhibiting the form which binds rolipram with a high affinity. Another way to state this is that the preferred
25 compounds will have an IC₅₀ ratio of about 0.1 or greater as regards the IC₅₀ for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC₅₀ for the form which binds rolipram with a low affinity.

30

A further refinement of this standard is that of one wherein the PDE4 inhibitor has an IC₅₀ ratio of about 0.1 or greater; said ratio is the ratio of the IC₅₀ value for competing with the binding of 1nM of [³H]R-rolipram to a form of PDE4 which binds rolipram with a high affinity over the IC₅₀ value for inhibiting the PDE4 catalytic activity of a form which binds rolipram with a low affinity using 1 μM[³H]-cAMP as the substrate.

Most preferred are those PDE4 inhibitors which have an IC₅₀ ratio of greater than 0.5, and particularly those compounds having a ratio of greater than 1.0. Preferred compounds are *cis* 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]; these are examples of compounds which bind preferentially to the low affinity binding site and which have an IC₅₀ ratio of 0.1 or greater.

Other compounds of interest include:

- 10 Compounds set out in U.S. patent 5,552,438 issued 03 September, 1996; this patent and the compounds it discloses are incorporated herein in full by reference. The compound of particular interest, which is disclosed in U.S. patent 5,552,438, is *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also known as cilomalast) and its salts, esters, pro-drugs or physical forms;
- 15 AWD-12-281 from elbion (Hofgen, N. *et al.* 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko in WO99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L.J. *et al.* Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12 (Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone (WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-Gulden; Pumafentrine, (-)-p-[(4aR*,10bS*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which is a mixed PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from Vernalis; or T-440 (Tanabe Seiyaku; Fuji, K. *et al.* J Pharmacol Exp Ther, 1998, 284(1): 30 162), and T2585.

Other possible PDE-4 and mixed PDE3/PDE4 inhibitors include those listed in WO01/13953, the disclosure of which is hereby incorporated by reference.

Suitable anticholinergic agents are those compounds that act as antagonists at the muscarinic receptor, in particular those compounds which are antagonists of the M₁ and M₂ receptors. Exemplary compounds include the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine, homatropine, hyoscyamine; these 5 compounds are normally administered as a salt, being tertiary amines. These drugs, particularly the salt forms, are readily available from a number of commercial sources or can be made or prepared from literature data via, to wit:

Atropine - CAS-51-55-8 or CAS-51-48-1 (anhydrous form), atropine sulfate - CAS-5908-99-6; atropine oxide - CAS-4438-22-6 or its HCl salt - CAS-4574-60-1 and methylatropine

10 nitrate - CAS-52-88-0.

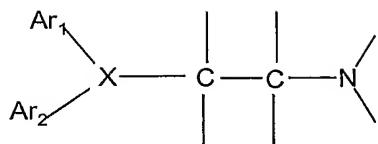
Homatropine - CAS-87-00-3, hydrobromide salt - CAS-51-56-9, methylbromide salt - CAS-80-49-9.

Hyoscyamine (*d, l*) - CAS-101-31-5, hydrobromide salt - CAS-306-03-6 and sulfate salt - CAS-6835-16-1.

15 Scopolamine - CAS-51-34-3, hydrobromide salt - CAS-6533-68-2, methylbromide salt- CAS-155-41-9.

Preferred anticholinergics include ipratropium (e.g. as the bromide), sold under the name Atrovent, oxitropium (e.g. as the bromide) and tiotropium (e.g. as the bromide) (CAS- 20 139404-48-1). Also of interest are: methantheline (CAS-53-46-3), propantheline bromide (CAS- 50-34-9), anisotropine methyl bromide or Valpin 50 (CAS- 80-50-2), clidinium bromide (Quarzan, CAS-3485-62-9), copyrrolate (Robinul), isopropamide iodide (CAS-71- 81-8), mepenzolate bromide (U.S. patent 2,918,408), tridihexethyl chloride (Pathilone, CAS-4310-35-4), and hexocyclium methylsulfate (Tral, CAS-115-63-9). See also 25 cyclopentolate hydrochloride (CAS-5870-29-1), tropicamide (CAS-1508-75-4), trihexyphenidyl hydrochloride (CAS-144-11-6), pirenzepine (CAS-29868-97-1), telenzepine (CAS-80880-90-9), AF-DX 116, or methocramine, and the compounds disclosed in WO01/04118, the disclosure of which is hereby incorporated by reference.

30 Suitable antihistamines (also referred to as H₁-receptor antagonists) include any one or more of the numerous antagonists known which inhibit H₁-receptors, and are safe for human use. All are reversible, competitive inhibitors of the interaction of histamine with H₁-receptors. The majority of these inhibitors, mostly first generation antagonists, have a core structure, which can be represented by the following formula:



This generalized structure represents three types of antihistamines generally available: ethanolamines, ethylenediamines, and alkylamines. In addition, other first generation 5 antihistamines include those which can be characterized as based on piperazine and phenothiazines. Second generation antagonists, which are non-sedating, have a similar structure-activity relationship in that they retain the core ethylene group (the alkylamines) or mimic the tertiary amine group with piperazine or piperidine. Exemplary antagonists are as follows:

10 Ethanolamines: carbinoxamine maleate, clemastine fumarate, diphenylhydramine hydrochloride, and dimenhydrinate.

Ethylenediamines: pyrilamine amleate, tripelennamine HCl, and tripelennamine citrate.

Alkylamines: chlropheniramine and its salts such as the maleate salt, and acrivastine.

15 Piperazines: hydroxyzine HCl, hydroxyzine pamoate, cyclizine HCl, cyclizine lactate, meclizine HCl, and cetirizine HCl.

Piperidines: Astemizole, levocabastine HCl, loratadine or its descarboethoxy analogue, and terfenadine and fexofenadine hydrochloride or another pharmaceutically acceptable salt.

Azelastine hydrochloride is yet another H_1 receptor antagonist which may be used in 20 combination with a PDE4 inhibitor.

Examples of preferred anti-histamines include methapyrilene and loratadine.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional 25 derivative thereof together with a PDE4 inhibitor.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic.

5 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an antihistamine.

10 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor and a corticosteroid.

15 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic and a PDE-4 inhibitor.

20 The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a physiologically acceptable diluent or carrier represent a further aspect of the invention.

25 The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

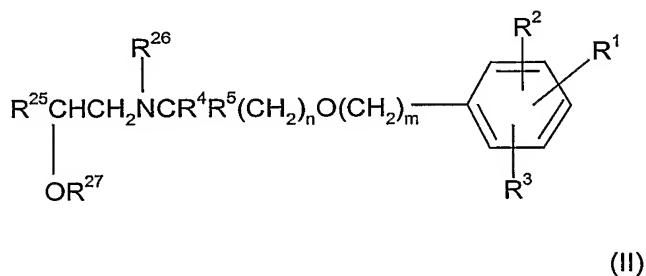
30 According to a further aspect of the invention, there is provided a process for preparing a compound of formula (I), or a salt, solvate, or physiologically functional derivative thereof which comprises a process (a), (b), (c) or (d) as defined below followed by the following steps in any order:

- 35 (i) optional removal of any protecting groups;
(ii) optional separation of an enantiomer from a mixture of enantiomers;
(iii) optional conversion of the product to a corresponding salt, solvate,
(iv) optional conversion of a group R¹, R² and/or R³ to another group R¹, R² and/or R³,

or physiologically functional derivative thereof.

In the following description of synthetic routes, R¹, R², R³, R⁴, R⁵, m and n are as defined for formula (I) and R²⁵, R²⁶, and R²⁷ are as defined for formula (II) below unless indicated
5 otherwise.

In one general process (a), a compound of formula (I), may be obtained by deprotection of a protected intermediate, for example of formula (II):

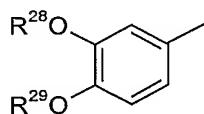


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or a salt or solvate thereof, wherein R¹, R², R³, R⁴, R⁵, m and n are as defined for the compounds of formula (I), and R²⁵ represents an optionally protected form of Ar and R²⁶ and R²⁷ each independently represents either hydrogen or a protecting group, provided
15 that the compound of formula (II) contains at least one protecting group..

Protected forms of the preferred groups Ar may be selected from:

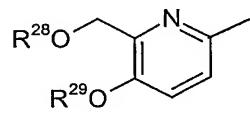
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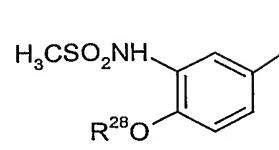
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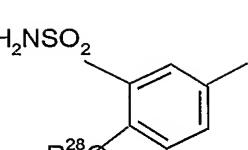
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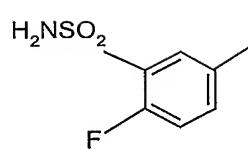
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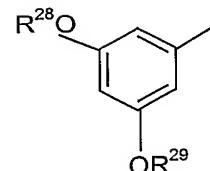
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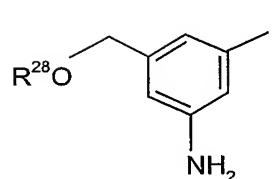
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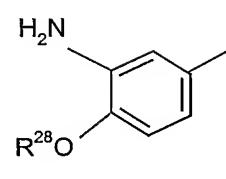
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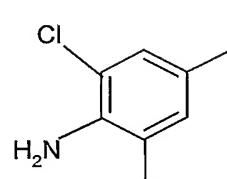
(viiia)



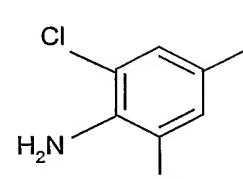
(viiixa)



(ixa)

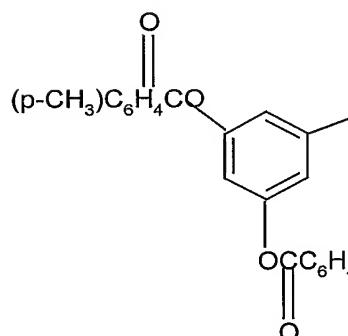


(xa)

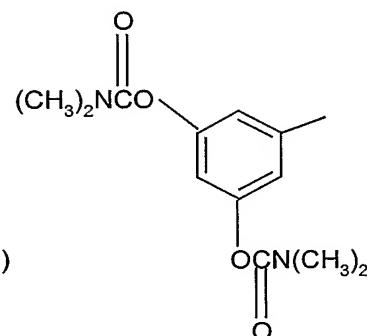


(xia)

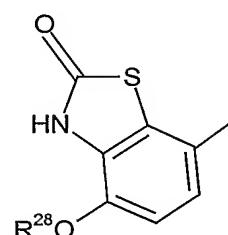
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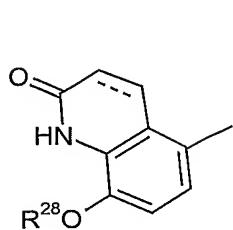
(xiia)



(xiiiia)



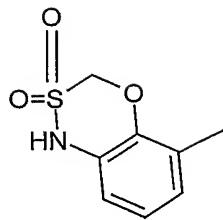
(xivaa)



(xva)

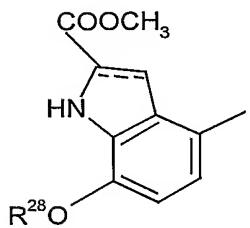


(xvia)

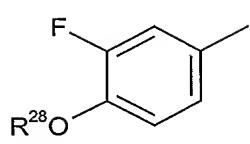


(xviiia)

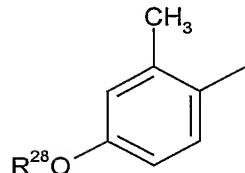
5



(xviiiia)



(xixia)



(xxa)

wherein R²⁸ and R²⁹ are each independently either hydrogen or a protecting group provided that at least one of R²⁸ and R²⁹ is a protecting group; and the dotted line in 10

(xviiiia) and (xxa) denotes an optional double bond.

Suitable protecting groups may be any conventional protecting group such as those described in "Protective Groups in Organic Synthesis" by Theodora W Greene and Peter G M Wuts, 3rd edition (John Wiley & Sons, 1999). Examples of suitable hydroxyl 15 protecting groups represented by R²⁸ and R²⁹ are esters such as acetate ester, aralkyl groups such as benzyl, diphenylmethyl, or triphenylmethyl, and tetrahydropyranyl. Examples of suitable amino protecting groups represented by R²⁶ include benzyl, α -methylbenzyl, diphenylmethyl, triphenylmethyl, benzyloxycarbonyl, tert-butoxycarbonyl, and acyl groups such as trichloroacetyl or trifluoroacetyl.

As will be appreciated by the person skilled in the art, use of such protecting groups may include orthogonal protection of groups in the compounds of formula (II) to facilitate the selective removal of one group in the presence of another, thus enabling selective 5 functionalisation of a single amino or hydroxyl function. For example, the –CH(OH) group may be orthogonally protected as – CH(OR²⁷) using, for example, a trialkylsilyl group such as triethylsilyl. A person skilled in the art will also appreciate other orthogonal protection strategies, available by conventional means as described in Theodora W Greene and Peter G M Wuts (see above).

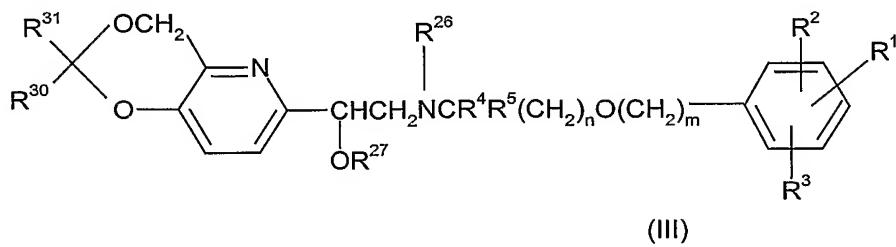
10

The deprotection to yield a compound of formula (I), may be effected using conventional techniques. Thus, for example, when R²⁸, R²⁹, and/or R²⁶ is an aralkyl group, this may be cleaved by hydrogenolysis in the presence of a metal catalyst (e.g. palladium on charcoal).

15

When R²⁸ and/or R²⁹ is tetrahydropyranyl this may be cleaved by hydrolysis under acidic conditions. Acyl groups represented by R²⁶ may be removed by hydrolysis, for example with a base such as sodium hydroxide, or a group such as trichloroethoxycarbonyl may be removed by reduction with, for example, zinc and acetic acid. Other deprotection 20 methods may be found in Theodora W Greene and Peter G M Wuts (see above).

In a particular embodiment of process (a), when R²⁵ represents a group (iiia) R²⁸ and R²⁹ may together represent a protecting group as in the compound of formula (III):



25

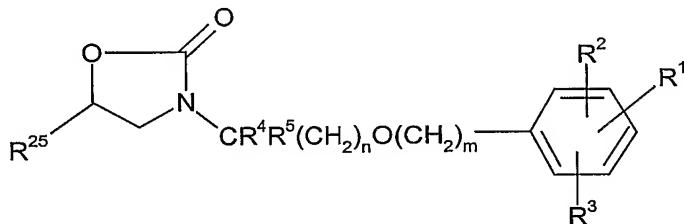
or a salt or solvate thereof, wherein R¹, R², R³, R⁴, R⁵, R²⁶, R²⁷, m and n are as defined for the compound of formula (II), and R³⁰ and R³¹ are independently selected from hydrogen, C₁₋₆alkyl, or aryl or R³⁰ and R³¹ together form a carbocyclic ring eg. containing from 5 to 7 30 carbon atoms.

The compound of formula (III) may be converted to a compound of formula (I), by hydrolysis with dilute aqueous acid, for example acetic acid or hydrochloric acid in a suitable solvent or by transketolisation in an alcohol, for example ethanol, in the presence 5 of a catalyst such as an acid (for example, toluenesulphonic acid) or a salt (such as pyridinium tosylate) at normal or elevated temperature.

It will be appreciated that the protecting groups R^{28} , R^{29} , R^{26} and R^{27} (including the cyclised protecting group formed by R^{30} and R^{31} as depicted in formula (III)) may be 10 removed in a single step or sequentially. The precise order in which protecting groups are removed will in part depend upon the nature of said groups and will be readily apparent to the skilled worker. Preferably, when R^{30} and R^{31} together form a protecting group as in formula (III) this protecting group is removed together with any protecting group on the $CH(OH)$ moiety, followed by removal of R^{26} .

15

Compounds of formulae (II) and (III) wherein R^{26} is hydrogen may be prepared from the corresponding compound of formula (IV).



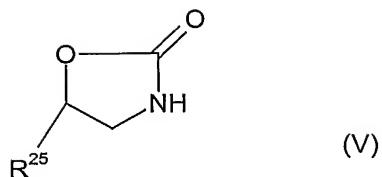
(IV)

20

or a salt or solvate thereof, wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^{25} , m and n are as defined for the compound of formula (II) or (III).

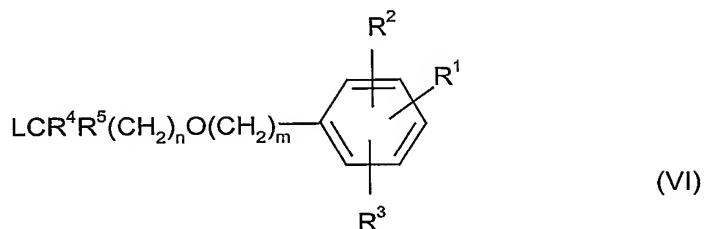
The conversion of a compound of formula (IV) to a compound of formula (II) or (III) may 25 be effected by treatment with a base, for example a non-aqueous base, such as potassium trimethylsilanolate, or an aqueous base such as aqueous sodium hydroxide, in a suitable solvent such as tetrahydrofuran.

Compounds of formula (IV) may be prepared by reacting a compound of formula (V):



with a compound of formula (VI):

5

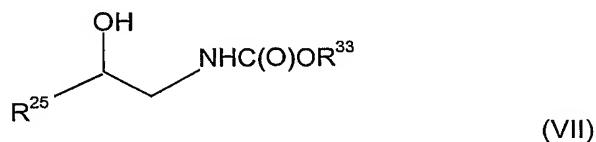


Wherein L is a leaving group such as halo (typically chloro, bromo or iodo) or a sulphonate (typically methanesulphonate) and R¹, R², R³, R⁴, R⁵, n and m are as defined
10 for compounds of formula (I).

The coupling of a compound of formula (V) with a compound of formula (VI) may be effected in the presence of a base, such as a metal hydride, for example sodium hydride, or an inorganic base such as cesium carbonate, in an aprotic solvent, for example N,N-
15 dimethylformamide.

Compounds of formula (V) may be prepared by ring closure of a compound of formula (VII):

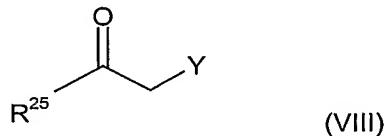
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wherein R²⁵ is as hereinbefore defined and R³³ is C₁₋₆alkyl, for example tert-butyl, or aryl, for example phenyl. The ring closure may be effected by treatment with a base, such as a metal hydride, for example sodium hydride, in the presence of an aprotic solvent, for example, N,N-dimethylformamide.

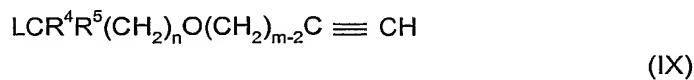
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The compound of formula (VII) may be prepared from the corresponding halide of formula (VIII):

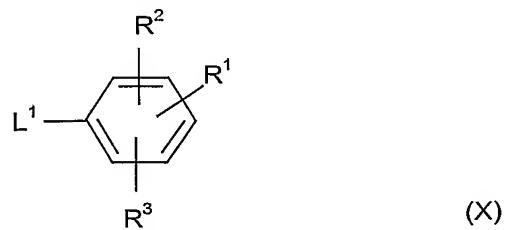


wherein R²⁵ and Y are as hereinbefore defined, by reaction with a protected amine
10 HN(COOR³³)₂, wherein R³³ is as defined for the compound of formula (VII), in the presence of an inorganic base such as cesium carbonate, followed by selective removal of one of the COOR³³ groups, for example by treatment with an acid such as trifluoroacetic acid, and subsequent reduction of the keto function by any suitable method, for example by treatment with borane, in the presence of a chiral catalyst, such as CBS-
15 oxazaborolidine, in a suitable solvent such as tetrahydrofuran.

A compound of formula (VI) may be prepared by coupling a compound of formula (IX):



20 wherein L is a leaving group as defined for formula (VI);
with a compound of formula (X):



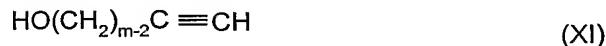
Wherein L¹ is a leaving group as hereinbefore defined for L and R¹, R², R³, are as hereinbefore defined, followed by reduction.

The coupling of a compound of formula (IX) with a compound of formula (X) is

- 5 conveniently effected in the presence of a catalyst system such as bis(triphenylphosphine)
palladium dichloride with an organic base such as a trialkylamine, for example
diisopropylethylamine, in a suitable solvent for example acetonitrile or dimethylformamide
or using the base as solvent. The resulting alkyne may then be reduced, either with or
without being isolated to form the desired saturated alcohol. The reduction may be
10 effected by any suitable method such a hydrogenation in the presence of a catalyst, for
example palladium/charcoal or platinum oxide.

Compounds of formula (X) are commercially available or may be prepared by methods
well known to the person skilled in the art.

- 15 A compound of formula (IX) may be prepared by reacting a compound of formula (XI):



- 20 Wherein m is as defined for formula (I) with a dihaloalkane of formula (XII):



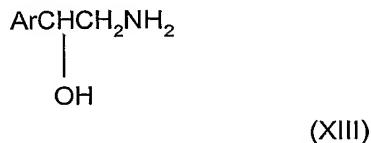
wherein R⁴, R⁵ and n are as hereinbefore defined and Y¹ and Y² each represent halo.

- 25 The reaction of compounds (XI) and (XII) is typically effected in the presence of an
inorganic base, such as sodium hydroxide under phase transfer conditions in the
presence of a tetra-alkylammonium salt, eg. tetrabutylammonium bromide.

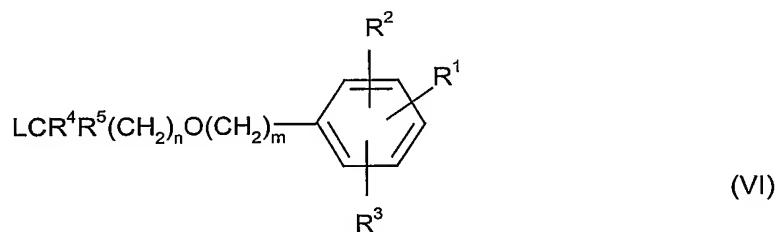
- 30 Compounds of formulae (XI) and (XII) are available commercially or can be prepared by
standard methods.

Alternatively, compounds of formula (II) and (III) wherein R²⁶ is either hydrogen or a protecting group may be prepared by any of the processes described hereinafter.

In a further process (b) a compound of formula (I) may be obtained by reacting a
5 compound of formula (XIII):



Wherein Ar is as defined above, with a compound of formula (VI):



10

Wherein L is a leaving group such as halo (typically chloro, bromo or iodo) or a sulphonate (typically methanesulphonate) and R¹, R², R³, R⁴, R⁵, n and m are as defined for compounds of formula (I).

15 The reaction of compounds of formula (XIII) and (VI) is optionally effected in the presence of an organic base, such as a trialkylamine, for example triethylamine, and in a suitable solvent, for example an amide such as DMF.

20 Compounds of formula (XIII) may be prepared by methods well known in the art. Thus for example they may be readily prepared by a person skilled in the art, from the corresponding halide of formula (XIV):



wherein Ar is as hereinbefore defined and Y is halo eg. bromo.

The conversion of a compound of formula (XIV) to a compound of formula (XIII) may be
5 effected by reaction with sodium azide in a suitable solvent, for example N,N-dimethylformamide, to give the corresponding compound wherein Y denotes N₃. The carbonyl group may then be reduced to the corresponding alcohol by any suitable method, for example by treatment with borane, in the presence of a chiral catalyst, such as (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole, in a
10 suitable solvent such as tetrahydrofuran. The azide group may be reduced to the corresponding amine group by any suitable method, for example by catalytic hydrogenation in the presence of a catalyst such as palladium/charcoal or platinum oxide.

Further details concerning preparation of compounds (XIII) wherein Ar is a group (iv) in
15 DE3524990; concerning the preparation of compounds (XIII) wherein Ar is a group (i), (vii), and (xv) in EP-A-162576; concerning the preparation of compounds (XIII) wherein Ar is a group (iii) in EP-A-22054; concerning the preparation of compounds (XIII) wherein Ar is a group (x) in GB2165542 and concerning the preparation of compounds (XIII) wherein Ar is a group (c) in GB2230523.
20

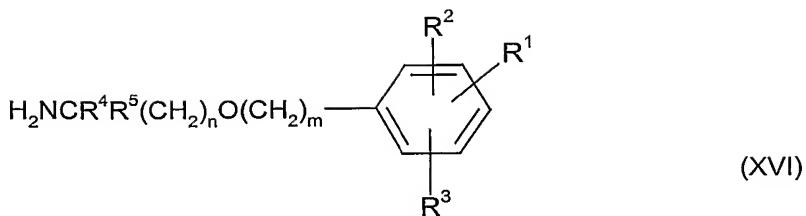
Compounds of formula (XIV) are known compounds or may readily be prepared by those skilled in the art using known methods.

In a further process (c) a compound of formula (I), may be prepared by reacting a
25 compound of formula (XV):



wherein L is a leaving group as hereinbefore defined, with an amine of formula (XVI):

30



The reaction may be effected using conventional conditions for such displacement reactions.

5

Compounds of formula (XV) may be prepared by methods known in the art.

Thus for example, compounds (XV) wherein Ar is a group (xv) may be prepared as described in EP-A-147719.

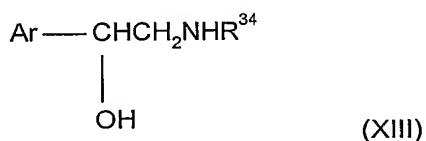
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Compounds of formula (XVI) may be prepared by reacting a compound of formula (VI) with an amine $R^{26}NH_2$, followed by removal of the protecting group R^{26} .

According to a further process (d) compounds of formula (I) wherein one of R^4 and R^5 represents hydrogen may be prepared by;

15

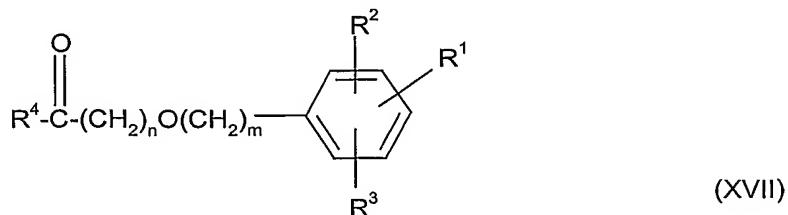
(i) reacting a compound of formula (XIII):



Wherein Ar is as hereinbefore defined and R^{34} represents hydrogen or a chiral auxiliary,

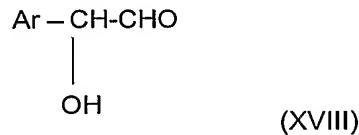
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with a compound of formula (XVII):

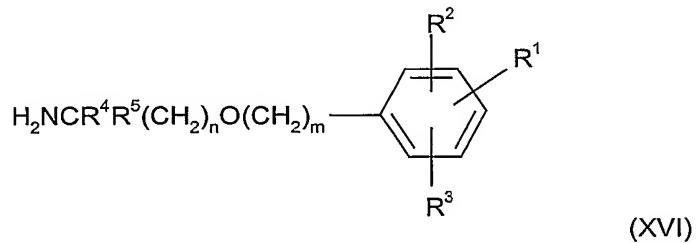


wherein R¹, R², R³, R⁴, n and m are as hereinbefore defined;
followed where necessary by removal of the chiral auxiliary R³⁴;

- 5 or (ii) reacting a compound of formula (XVIII):



wherein Ar is as hereinbefore defined; with an amine of formula (XVI):



10

as hereinbefore defined,

under conditions suitable to effect reductive amination, for example in the presence of a reducing agent such as a borohydride, typically tetramethylammonium (triacetoxy) 15 borohydride.

When process (di) involves use of a chiral auxiliary this is preferably the S-isomer and/or the R-isomer of phenyl glycitol. The reaction may be effected as described in International Application Number WO/0196278.

20

A compound of formula (XVII) may be prepared by methods known in the art, for example via a compound of formula (VI) as hereinbefore defined.

25 A compound of formula (XVIII) may also be prepared from a corresponding alcohol, which may itself be obtained from a compound of formula (XV) as hereinbefore defined, using standard methods well known to those skilled in the art.

It will be appreciated that in any of the routes (a) to (d) described above, the precise order of the synthetic steps by which the various groups and moieties are introduced into the molecule may be varied. It will be within the skill of the practitioner in the art to ensure
5 that groups or moieties introduced at one stage of the process will not be affected by subsequent transformations and reactions, and to select the order of synthetic steps accordingly. It will also be appreciated that in the processes (b), (c) and (d) appropriate protecting groups may be employed if necessary and/or desired and removed at any suitable stage of the synthesis, eg. in the last stage, as described in process (a).

10

The enantiomeric compounds of the invention may be obtained (i) by separation of the components of the corresponding racemic mixture, for example, by means of a chiral chromatography column, enzymic resolution methods, or preparing and separating suitable diastereoisomers, or (ii) by direct synthesis from the appropriate chiral
15 intermediates by the methods described above.

Optional conversions of a compound of formula (I), to a corresponding salt may conveniently be effected by reaction with the appropriate acid or base. Optional conversion of a compound of formula (I), to a corresponding solvate or physiologically
20 functional derivative may be effected by methods known to those skilled in the art.

According to a further aspect, the present invention provides novel intermediates for the preparation of compounds of formula (I), for example:
compounds of formula

25

For a better understanding of the invention, the following Examples are given by way of illustration.

SYNTHETIC EXAMPLES

30

Throughout the examples, the following abbreviations are used:

LC: Liquid Chromatography

LCMS: Liquid Chromatography Mass Spectrometry

HPLC: High Performance Liquid Chromatography

35 RT: retention time

DCM: dichloromethane

IMS: industrial methylated spirits

EtOAc: ethyl acetate

EtOH: ethanol

5 DMAP: N,N-Dimethylaminopyridine

DMF: N,N-Dimethylformamide

MeOH: methanol

THF: tetrahydrofuran

IMS: Industrial methylated spirits

10 h: hour(s)

min: minute(s)

All temperatures are given in degrees celcius.

Flash silica gel refers to Merck Art No. 9385; silica gel refers to Merck Art No. 7734

Biotage refers to prepacked silica gel cartridges containing KP-Sil run on flash 12i
15 chromatography module.

Solid Phase Extraction (SPE) columns are pre-packed cartridges used in parallel purifications, normally under vacuum. These are commercially available from Varian.

SCX cartridges are Ion Exchange SPE columns where the stationary phase is polymeric benzene sulfonic acid. These are used to isolate amines.

20

LC was conducted on a Luna C18(2) column (5cm x 2.0mm ID) eluting with 0.05%v/v trifluoroacetic acid in water (solvent A) and 0.05%v/v trifluoroacetic acid in acetonitrile (solvent B) using the following elution gradient 0.00-8.00 min 0%B, 8.00-8.01 min 95%B, 8.01-10.00 min 0%B at a flow rate of 1.0 ml/min with a column temperature of 40°C.

25

LCMS was conducted on a Supelcosil LCABZ+PLUS column (3.3cm x 4.6mm ID) eluting with 0.1% HCO₂H and 0.01M ammonium acetate in water (solvent A) and 0.05% HCO₂H 5% water in acetonitrile (solvent B), using the following elution gradient 0.0-7min 0%B, 0.7-4.2 min 100%B, 4.2-5.3 min 0%B, 5.3-5.5min 0%B at a flow rate of 3mL/min. The 30 mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES+ve and ES-ve).

Preparative mass directed HPLC was conducted on a Waters FractionLynx system comprising of a Waters 600 pump with extended pump heads, Waters 2700 autosampler, 35 Waters 996 diode array and Gilson 202 fraction collector on a 10 cm X 2.54 cm ID ABZ+

column, eluting with 0.1% formic acid in water (solvent A) and 0.1% formic acid in acetonitrile (solvent B), using the following elution gradient: 0.0-1.0 min 15%B, 1.0-10.0 min 55%B, 10.0-14.5 min 99%B, 14.5-14.9 min 99%B, 14.9-15.0 min 15%B at a flow rate of 20 ml/min and detecting at 200-320 nm at room temperature. Mass spectra were recorded on Micromass ZMD mass spectrometer using electrospray positive and negative mode, alternate scans. The software used was *MassLynx* 3.5 with *OpenLynx* and *FractionLynx* options.

10 EXAMPLE 1

8-Hydroxy-5-((1R)-1-hydroxy-2-{[6-(4-phenylbutoxy)hexyl]amino}ethyl)quinolin-2(1H)-one acetate

(i) 8-(Benzylxy)-5-[(1R)-2-bromo-1-hydroxyethyl]quinolin-2(1H)-one

15 A solution of [(*R*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*] [1,3,2]-oxazaborole] (1M, 424µL) in THF (2ml) was added to borane dimethylsulfide complex (2M, 212.7µl) in THF (15ml) and stirred at 0°C for 10 min. The reaction mixture was cooled to -10°C and treated with a solution of 8-benzylxy-5-bromoacetylcarbostyryl (EP 147719A2) (791mg) in THF (16ml) over 20 min. Further borane dimethylsulfide complex (1.28ml) was added over 4 h at 0°C. The reaction mixture was stirred for a further hour at 20 0°C prior to quenching with methanol and 1N HCl(aq). The reaction mixture was partitioned between water and ethyl acetate. The organic phase was dried and concentrated *in vacuo*. The residue was triturated with hexane-ethyl acetate to afford *the title compound* (700mg). Rf (EtOAc) 0.47

25

(ii) 8-(Benzylxy)-5-[(1R)-2-bromo-1-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]quinolin-2(1H)-one

A suspension of 8-(benzylxy)-5-[(1R)-2-bromo-1-hydroxyethyl]quinolin-2(1*H*)-one (100mg) and pyridinium tosylate (14mg) in dry DCM (2ml) was treated with 2,3-30 dihydropyran (61.2µl) and stirred at 22°C for 18h. The reaction mixture was concentrated *in vacuo* and purified by chromatography (Hexane-EtOAc 2:1, biotage) to give *the title compound* (77mg). Rf [EtOAc-Hexane (1:1)] 0.54

(iii) 8-(Benzylxy)-5-[(1R)-2-{benzyl[6-(4-phenylbutoxy)hexyl]amino}-1-(tetrahydro-2*H*-

35 pyran-2-yloxy)ethyl]quinolin-2(1*H*)-one

8-(Benzylxylo)-5-[(1*R*)-2-bromo-1-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]quinolin-2(*1H*)-one (100mg), *N*-benzyl-6-(4-phenylbutoxy)hexan-1-amine (*Tetrahedron Letters*. 1994, **35**, 9375) (112mg) and diisopropylethylamine (77 μ l) were heated in a reacti-vial at 120°C for 4 h prior to cooling to room temperature. The mixture was purified by chromatography (Hexane-EtOAc 2:1, biotage) afforded *the title compound* (85mg). LCMS RT= 3.46min

5
(iv) 8-(Benzylxylo)-5-((1*R*)-2-{benzyl[6-(4-phenylbutoxy)hexyl]amino}-1-hydroxyethyl)quinolin-2(*1H*)-one

A solution of 8-(benzyloxy)-5-[(1*R*)-2-{benzyl[6-(4-phenylbutoxy)hexyl]amino}-1-tetrahydro-2*H*-pyran-2-yloxy)ethyl]quinolin-2(*1H*)-one (80mg) in acetic acid (4ml), THF (2ml) and water (1ml) was heated at 80°C for 17h prior to concentration *in vacuo*. The residue was purified by chromatography (Hexane-EtOAc 2:1, biotage) to give *the title compound* (33.5mg).

LCMS RT= 3.22min

15

(v) 8-Hydroxy-5-((1*R*)-1-hydroxy-2-{[6-(4-phenylbutoxy)hexyl]amino}ethyl)quinolin-2(*1H*)-one acetate

A solution of 8-(benzyloxy)-5-((1*R*)-2-{benzyl[6-(4-phenylbutoxy)hexyl]amino}-1-hydroxyethyl)quinolin-2(*1H*)-one (33mg) in ethanol (15ml) and acetic acid (0.4ml) was stirred under hydrogen in the presence of palladium on charcoal (10mg) for 4 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by chromatography (SPE, gradient from DCM to DCM-MeOH-NH₃(aq) 100:10:1) to give *the title compound* (19.5mg).

LCMS RT= 2.66 min ES+ve 452 (MH)⁺

25

EXAMPLE 2

3-{4-[6-{[(2*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}hexyl]oxy}butyl}benzenesulfonamide acetate

30
(i) 6-Bromohexyl but-3-ynyl ether

A mixture of 50% w/v aqueous sodium hydroxide (2500ml), 1,6-dibromohexane (2610g) and tetra-butylammonium bromide (25g) was warmed to 50°C, with stirring. But-3-yn-1-ol (500g) was then added to the reaction mixture at such a rate as to ensure the content's temperature did not exceed 65°C. The reaction was left at 50°C overnight before being cooled to room temperature. Tert-butyl methyl ether (2500ml) and brine (2000ml) was

added to the cooled mixture and the layers allowed to separate. The ethereal layer was washed with water (2x2000ml), brine (1x2000ml), and then dried over anhydrous MgSO₄. The solution was filtered and concentrated under reduced pressure to give crude product as a liquid. This was further purified by fractional distillation using a 60cm vacuum jacketed Vigreux column at ca. 0.5mbar. The product was obtained in the fraction which boiled at 92-98°C, to give the *title compound* (518g), LC RT = 6.16 min.

5 (ii) 3-{4-[(6-Bromohexyl)oxy]but-1-ynyl}benzenesulfonamide

A mixture of 3-bromo-benzenesulfonamide (625g), 6-bromohexyl but-3-ynyl ether (850.1g), bis(triphenylphosphine)palladium (II) chloride (62.5g), triphenylphosphine (18.1g) and triethylamine (536.3g) in tetrahydrofuran (6250ml) was stirred under an atmosphere of nitrogen for 20 min. Copper (I) iodide (12.5g) was then added to give a dark red/brown mixture that was heated to 50°C for 23h. The reaction mixture was then cooled to room temperature and filtered through a short silica pad (1000g). The pad was washed with additional tetrahydrofuran (15.6L) and the resulting solution then concentrated under reduced pressure to give crude product (1382g) as a viscous oil. This was purified by chromatography (7kg silica) eluting with petroleum ether-ethyl acetate (5:1) followed by petroleum ether-ethyl acetate (2:1) to give the *title compound* (932.9g) as an oil, LC RT = 5.69min.

10

(iii) 3-{4-[(6-Bromohexyl)oxy]butyl}benzenesulfonamide

3-{4-[(6-Bromohexyl)oxy]but-1-ynyl}benzenesulfonamide (627g) in IMS (1900ml) was stirred with activated charcoal (314g) at room temperature for 2h and then filtered through a short pad of Celite. The filter pad was washed with IMS (4300ml) and the filtrate transferred to a hydrogenation vessel. 5% Platinum on Charcoal (520.1g, ~50% water) was added and the reaction mixture was then stirred under an atmosphere of hydrogen (0.2 bar) at 20°C for 6 h. The mixture was then filtered through a short pad of Celite and concentrated under reduced pressure to give the *title compound* (499g) as a solid, LC RT = 5.66 min.

15

(iv) 3-(4-[(6-(Benzylamino)hexyl)oxy]butyl)benzenesulfonamide

3-[4-(6-Bromo-hexyloxy)-butyl]benzenesulfonamide (1.0g) in toluene (4ml) was added dropwise to benzylamine (0.65g) and the resulting mixture heated at 80°C for 6h. The

mixture was then cooled and 20% aqueous sodium hydroxide solution (50ml) was added. The resulting mixture was extracted with ethyl acetate and the combined organic layers evaporated to dryness *in vacuo*. The residual oil was then purified by chromatography (DCM-IMS-NH₃(aq) 100:10:1) to give the *title compound* (0.54g) LC RT = 3.89 min.

5

(v) 3-(4-{[6-(Benzyl{(2R)-2-[8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-
acetyl}amino)hexyl]oxy}butyl)benzenesulfonamide

A solution of 8-benzyloxy-5-bromoacetylcarbostyryl (100mg) (EP 147719A2) in dry DMF was treated with 3-(4-{[6-(benzylamino)hexyl]oxy}butyl)benzenesulfonamide (172mg) and 10 diisopropylethylamine (94.5μl) and stirred at 40°C for 2h prior to concentration *in vacuo*. The residue was purified by chromatography (SPE, gradient from DCM to DCM-MeOH-NH₃(aq) 100:10:1) to give the *title compound* (56mg).

LCMS RT= 2.95 min.

15

(vi) 3-(4-{[6-(Benzyl{(2R)-2-[8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-
hydroxyethyl}amino)hexyl]oxy}butyl)benzenesulfonamide

A solution of [(*R*)-tetrahyro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*] [1,3,2]-oxazaborole] (108μL) in THF (1ml) was added to borane dimethylsulfide complex in THF (2M, 54μl) and stirred at 0°C for 10 min. The reaction mixture was cooled to -10°C and 20 treated with a solution of 3-(4-{[6-(benzyl{(2R)-2-[8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-acetyl}amino)hexyl]oxy}butyl)benzenesulfonamide (64mg) in THF (3ml). The reaction mixture was stirred for 16h at 0°C prior to quenching with 2N HCl(aq). The reaction mixture was partitioned between 2N HCl(aq) and ethyl acetate. The organic phase was dried and concentrated *in vacuo*. The residue was purified by chromatography (biotage, DCM-MeOH-NH₃(aq) 400:10:1) to give the *title compound* (10mg).

25

LCMS RT= 2.91 min.

(vii) 3-{4-[{6-(2R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-
yl)ethyl}amino}hexyl]oxy}butyl)benzenesulfonamide acetate

30 A solution of 3-(4-{[6-(Benzyl{(2R)-2-[8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-
hydroxyethyl}amino)hexyl]oxy}butyl)benzenesulfonamide (10mg) in ethanol (10ml) and acetic acid (0.1ml) was stirrer under hydrogen in the presence of palladium on charcoal (5mg) for 2 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by chromatography (SPE, gradient from DCM to DCM-MeOH-NH₃(aq)

100:10:1) and freeze-dried from water-acetic acid to give *the title compound* (5.8mg).
LCMS RT= 2.28 min ES+ve 532 (MH)⁺

EXAMPLE 3

5 5-Hydroxy-8-(1-hydroxy-2-[{[6-(4-phenylbutoxy)hexyl]amino}ethyl]-2H-1,4-benzoxazin-3(4H)-one acetate

(i) 5-(Benzyl)-8-(2-{benzyl}[6-(4-phenylbutoxy)hexyl]amino)-1-hydroxyethyl)-2H-1,4-benzoxazin-3(4H)-one

10 A solution of 5-(benzyloxy)-8-(dihydroxyacetyl)-2H-1,4-benzoxazin-3(4H)-one (DE 3134590 A1) (150mg) in dry DCM (2ml) was treated with acetic acid and *N*-benzyl-6-(4-phenylbutoxy)hexan-1-amine (320mg) (*Tetrahedron Letters*. 1994, 35, 9375) and stirred for 4hr. Sodium triacetoxyborohydride (216mg) was added and the reaction mixture stirred at room temperature for 3 days. Sodium borohydride (35mg) in methanol (2ml) was added and stirring continued for a further 2h. The reaction mixture was quenched with water and partitioned between water and DCM. The organic phase was dried and concentrated *in vacuo*. The residue was purified by chromatography (Hexane-EtOAc, SPE) to give *the title compound* as a mixture with 5-(benzyloxy)-8-(benzyl[6-(4-phenylbutoxy)hexyl]amino)acetyl)-2H-1,4-benzoxazin-3(4H)-one (81.6mg).

15

20 LCMS RT= 3.24 min.

(ii) 5-Hydroxy-8-(1-hydroxy-2-[{[6-(4-phenylbutoxy)hexyl]amino}ethyl]-2H-1,4-benzoxazin-3(4H)-one acetate

25 A solution of 5-(benzyloxy)-8-(2-{benzyl}[6-(4-phenylbutoxy)hexyl]amino)-1-hydroxyethyl)-2H-1,4-benzoxazin-3(4H)-one (82mg) in ethanol (10ml) and ethyl acetate (2ml) was stirred under hydrogen in the presence of palladium on charcoal (50mg) for 8 h. The reaction mixture was filtered and concentrated *in vacuo*. Mass directed auto-preparative chromatography afforded *the title compound* (13.7 mg). LCMS RT= 2.62 min ES+ve 456 (MH)⁺

30

EXAMPLE 4

3-{4-[{2-Hydroxy-2-(5-hydroxy-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-8-yl)ethyl]amino}hexyl]oxy}butyl}benzenesulfonamide

(i) 3-(4-{[6-(Benzyl{2-[5-(benzyloxy)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-8-yl]-2-hydroxyethyl}amino)hexyl]oxy}butyl)benzenesulfonamide

Prepared by methods similar to that described for Example 3i as a mixture with 3-(4-{[6-(benzyl{2-[5-(benzyloxy)-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-8-yl]-2-

5 acetyl}amino)hexyl]oxy}butyl)benzenesulfonamide (22.3mg).

LCMS RT= 2.83 min

(ii) 3-{4-[(6-{[2-Hydroxy-2-(5-hydroxy-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-8-yl)ethyl}amino)hexyl]oxy}butyl)benzenesulfonamide

10 Prepared by methods similar to that described for Example 3ii LCMS RT= 2.32 min
ES+ve 536 (MH)⁺

EXAMPLE 5

4-Hydroxy-7-((1R)-1-hydroxy-2-{[6-(4-phenylbutoxy)hexyl]amino}ethyl)-1,3-benzothiazol-

15 2(3H)-one formate

(i) 7-Acetyl-4-methoxy-1,3-benzothiazol-2(3H)-one

A solution of 4-methoxy-1,3-benzothiazol-2(3H)-one (DE 3017977 A1) (1.92g) in dry dichloromethane (50ml) was cooled to ~5°C under nitrogen. Acetyl chloride (1.43ml) and 20 aluminium chloride (3.43g) were added in one portion, and stirred for 2h at RT. The reaction was quenched carefully with water, followed by addition of 2N HCl and dichloromethane. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with brine and dried (Na₂SO₄) and evaporated in *vacuo* to give *the title compound* (1.92g). LCMS RT=2.50min

25

(ii) 7-Acetyl-4-hydroxy-1,3-benzothiazol-2(3H)-one

A mixture of 7-acetyl-4-methoxy-1,3-benzothiazol-2(3H)-one (1.2g), pyridine hydrochloride (2.77g), in dry 1-methyl-2-pyrrolidone(6ml), was heated at 190°C in a microwave reactor for 90 min. The reaction mixture was cooled to room temperature, and diluted with water. 30 The precipitated solid was collected by filtration, washed with water and dried under vacuum at 40°C to give *the title compound* (1.07g). LCMS RT= 2.46min.

(iii) 7-Acetyl-4-(benzyloxy)-1,3-benzothiazol-2(3H)-one.

To a solution of 7-acetyl-4-hydroxy-1,3-benzothiazol-2(3H)-one (153mg), in dry THF (3ml) 35 and dry DMF (0.5ml) under nitrogen, was added N,N-diisopropylethylamine (0.13ml) and

benzyl bromide (0.09ml), and the mixture stirred for 72h. Water (10ml) was added and the mixture extracted with ethyl acetate. The organic phases were combined, washed with brine, dried (MgSO_4), and evaporated *in vacuo*. The residue was purified on a 5g silica SPE cartridge, eluting with a stepped gradient of 10% to 50% ethyl acetate -cyclohexane mixtures, to give the title compound (68mg). LCMS RT= 3.14min.

5 (iv) 4-(BenzylOxy)-7-(bromoacetyl)-1,3-benzothiazol-2(3H)-one

To a solution of 7-acetyl-4-(benzylOxy)-1,3-benzothiazol-2(3H)-one (68mg) in dry THF (3ml) under nitrogen, was added phenyltrimethylammonium tribromide (90mg) and the mixture heated at 80°C under nitrogen for 2h. The mixture was diluted with water, extracted with ethyl acetate, dried (MgSO_4), filtered and evaporated *in vacuo*. The residue was purified on a 5g silica SPE cartridge, eluting with stepped gradient of 10% to 100% ethyl acetate - cyclohexane mixtures, to give *the title compound* (49mg).

10 LCMS RT=3.13min.

15 (v) 4-(BenzylOxy)-7-[(1R)-2-bromo-1-hydroxyethyl]-1,3-benzothiazol-2(3H)-one

A solution of [(*R*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-c] [1,3,2]-oxazaborole] (22 μ l of 1M in toluene) in dry THF(1ml) was cooled to -5°C, stirring under nitrogen. Borane-methyl sulfide complex (2M solution in THF, 11 μ l) was added and stirred for 10 min at -5°C. A solution of 4-(benzylOxy)-7-(bromoacetyl)-1,3-benzothiazol-2(3H)-one (47mg) in dry THF (1.5ml) was added dropwise and then another 66 μ l of borane-methyl sulfide complex (2M solution in THF). The reaction mixture was left for 72 h at less than 5°C and then partitioned between 2N HCl and ethyl acetate. The organic solution was dried (MgSO_4), filtered and evaporated *in vacuo*. The residue was purified on a 5g silica SPE cartridge, eluting with a stepped gradient of 10% to 25% ethyl acetate - cyclohexane mixtures to give *the title compound* (33mg). LCMC RT= 3.19min.

20 (vi) 4-(BenzylOxy)-7-[(1R)-2-bromo-1-[tetrahydro-2*H*-pyran-2-yloxy]ethyl]-1,3-benzothiazol-2(3H)-one

25 To a stirred solution of 4-(benzylOxy)-7-[(1*R*)-2-bromo-1-hydroxyethyl]-1,3-benzothiazol-2(3*H*)-one (31mg) in dry DCM (5ml) under nitrogen, was added pyridinium *p*-toluenesulphonate (5mg), followed by 3,4-dihydro-2*H*-pyran (30 μ l). The mixture was evaporated *in vacuo* after 18h and purified on a 2g silica SPE cartridge, eluting with a stepped gradient 10% to 100% DCM - cyclohexane mixtures, to give *the title compound* (42mg). LCMS RT= 3.72 and 3.78min.

(vii) 4-(Benzyl)-7-((1R)-2-{benzyl[6-(4-phenylbutoxy)hexyl]amino}-1-[tetrahydro-2H-pyran-2-yloxy]ethyl}-1,3-benzothiazol-2(3H)-one

A mixture of 4-(benzyloxy)-7-((1R)-2-bromo-1-[tetrahydro-2H-pyran-2-yloxy]ethyl)-1,3-benzothiazol-2(3H)-one (42mg), N,N-diisopropylethylamine (32μl), and N-benzyl-6-(4-phenylbutoxy)hexan-1-amine (*Tetrahedron Letters.* 1994, 35, 9375) (47.5mg), was heated at 120°C in a reacti-vial for 18 h. The mixture was dissolved in DCM and purified on a 12g biotage cartridge, eluting with 15% ethyl acetate - cyclohexane mixture to give *the title compound* (10mg). LCMS RT= 3.62 and 3.66min.

10

(viii) 4-(Benzyl)-7-((1R)-2-{benzyl[6-(4-phenylbutoxy)hexyl]amino}-1-hydroxyethyl)-1,3-benzothiazol-2(3H)-one

To a solution of 4-(benzyloxy)-7-((1R)-2-{benzyl[6-(4-phenylbutoxy)hexyl]amino}-1-[tetrahydro-2H-pyran-2-yloxy]ethyl)-1,3-benzothiazol-2(3H)-one (10mg) in dry DCM (1ml) and methanol (0.1ml) stirring under nitrogen, was added p-toluenesulphonic acid (10mg). After 18 h 2N sodium bicarbonate was added and the mixture extracted with DCM. The organic solution was diluted with cyclohexane and the mixture purified on a 5g silica SPE cartridge to give *the title compound* (7.4mg). LCMS RT= 3.13min.

20

(ix) 4-Hydroxy-7-((1R)-1-hydroxy-2-{[6-(4-phenylbutoxy)hexyl]amino}ethyl)-1,3-benzothiazol-2(3H)-one formate

4-(Benzyl)-7-((1R)-2-{benzyl[6-(4-phenylbutoxy)hexyl]amino}-1-hydroxyethyl)-1,3-benzothiazol-2(3H)-one (7.4mg) was dissolved in 98% formic acid (0.5ml) and palladium black catalyst (4mg) added. After stirring for 8 h, the catalyst was removed by filtration through celite and the filtrate evaporated *in vacuo*. The residue was purified on mass directed autoprep, to give *the title compound* (0.51mg). LCMS RT= 2.95min. ES+ve 459 (M+H)⁺

EXAMPLE 6

30 4-Hydroxy-7-(1-hydroxy-2-{[6-(4-phenylbutoxy)hexyl]amino}ethyl)-1,3-benzothiazol-2(3H)-one formate

(i) 7-Acetyl-2-oxo-2,3-dihydro-1,3-benzothiazol-4-yl benzyl carbonate

A mixture of 7-acetyl-4-hydroxy-1,3-benzothiazol-2(3H)-one (209mg) in dry THF (5ml) and DCM (5ml) with pyridine (0.2ml), stirring under nitrogen, was cooled to -10°C and

benzylchloroformate (0.37mls) was added. After 18h stirring at room temperature, the mixture was diluted with water and extracted into DCM. The solution was dried (MgSO_4), filtered, and evaporated *in vacuo*. The residue was purified on a 10g silica SPE cartridge, eluting with a stepped gradient of 25% to 100% ethyl acetate - cyclohexane mixtures, to give the title compound (280mg). LCMS RT= 3.19min.

5 (ii) Benzyl 7-(bromoacetyl)-2-oxo-2,3-dihydro-1,3-benzothiazol-4-yl carbonate

To a solution of 7-acetyl-2-oxo-2,3-dihydro-1,3-benzothiazol-4-yl benzyl carbonate (280mg) in dry THF (20ml) stirring under nitrogen, was added phenyltrimethylammonium tribromide (330mg). The mixture was heated at 80°C for 2 h and then diluted with water, extracted with ethyl acetate, dried (MgSO_4), filtered, and evaporated *in vacuo*. The residue was purified on a 40g silica biotage cartridge and eluted with 20% ethyl acetate - cyclohexane to give the title compound (186mg). LCMS RT=3.43min.

10 15 (iii) 7-({Benzyl[6-(4-phenylbutoxy)hexyl]amino}acetyl)-4-hydroxy-1,3-benzothiazol-2(3H)-one

To a solution of benzyl 7-(bromoacetyl)-2-oxo-2,3-dihydro-1,3-benzothiazol-4-yl carbonate (50mg) in dry DMF (1ml) stirring under nitrogen was added N-benzyl-6-(4-phenylbutoxy)hexan-1-amine (*Tetrahedron Letters*. 1994, 35, 9375) (60mg) and N,N-diisopropylethylamine (32 μ l). After stirring at 40°C for 2h, 2N HCl was added and the mixture extracted with ethyl acetate. The solution was dried (MgSO_4), filtered and evaporated *in vacuo*. The residue was purified on a 5g silica SPE cartridge, eluting with a stepped gradient of 2% to 10% methanol - dichloromethane mixtures to give the title compound (50mg). LCMS RT=3.14min.

20 25 (iv) 4-Hydroxy-7-({[6-(4-phenylbutoxy)hexyl]amino}acetyl)-1,3-benzothiazol-2(3H)-one

A solution of 7-({benzyl[6-(4-phenylbutoxy)hexyl]amino}acetyl)-4-hydroxy-1,3-benzothiazol-2(3H)-one (100mg) in dry ethanol (10ml) and acetic acid (0.5ml) was added to 10% Pd/C catalyst (40mg) and stirred under hydrogen for 20 h. The catalyst was collected by filtration through celite and the filtrate evaporated *in vacuo*. The residue was purified on SCX and then silica SPE cartridge, eluting with a stepped gradient of 1-10% methanol- dichloromethane mixtures, to give the title compound (9mg). LCMS RT=2.81min.

(v) 4-Hydroxy-7-(1-hydroxy-2-{{[6-(4-phenylbutoxy)hexyl]amino}ethyl}-1,3-benzothiazol-2(3H)-one formate

Sodium borohydride (4mg) was added to a solution of 4-hydroxy-7-({[6-(4-phenylbutoxy)hexyl]amino}acetyl)-1,3-benzothiazol-2(3H)-one (9mg) in dry ethanol (2ml).

5 The mixture was stirred under nitrogen for 2 h, and then quenched with water and evaporated in *vacuo*. The residue was purified by mass directed autoprep. to give *the title compound* (1.5mg). LCMS RT= 2.74min, ES+ve 459 (M+H)⁺

10 EXAMPLE 7

3-{4-[(2R)-2-(3-Fluoro-4-hydroxyphenyl)-2-hydroxyethyl]amino}hexyl]oxy]butyl}benzenesulfonamide formate

i) 2-Azido-1-[4-(benzyloxy)-3-fluorophenyl]ethanone

15 A solution of 2-bromo-1-[4-(benzyloxy)-3-fluorophenyl]ethanone (*J. Med. Chem.* **1980**, 23, 738-744) (1g) in dry DMF (2.5mL) was cooled to 15°C and treated portionwise with sodium azide (220mg). After complete addition the reaction mixture was stirred for a further 1h. The reaction mixture was partitioned between EtOAc and water. The organic phase was washed with water and the combined aqueous phase back extracted with 20 EtOAc. The combined organic phase was washed with sat. NaHCO₃_(aq) three times and the combined washes back extracted with EtOAc. The combined organic phase was washed with brine, dried and concentrated in *vacuo*. The residue was purified by column chromatography on silica, eluting with hexane-EtOAc (4:1 and 2:1) to give *the title compound* (810mg). LCMS RT= 3.61 min.

25

ii) (1R)-2-Azido-1-[4-(benzyloxy)-3-fluorophenyl]ethanol

Borane-dimethylsulphide solution in THF (2M, 0.03 mL) was added to a solution of (R)-2-methyl-CBS-oxazaborolidine in toluene (1M, 0.06mL) at 0°C with stirring. The reaction mixture was stirred for 15 min prior to the dropwise addition of a solution of 2-azido-1-[4-(benzyloxy)-3-fluorophenyl]ethanone (100mg) in THF. Further Borane-dimethylsulphide in THF (2M, 0.03mL) was added dropwise and the reaction mixture stirred at 0°C for 2h. 2M HCl_(aq) (2mL) was added dropwise and the reaction mixture stirred for 10 min prior to partitioning the reaction mixture between ether and water. The organic phase was washed twice with 2M HCl_(aq), three times with sat. NaHCO₃_(aq), water and brine. The 30 organic phase was dried and concentrated in *vacuo*. The residue was purified by column 35

chromatography on silica gel, eluting with DCM to give *the title compound* (470mg). LCMS RT= 3.36 min.

iii) (1R)-2-Amino-1-[4-(benzyloxy)-3-fluorophenyl]ethanol

5 A solution of (1R)-2-azido-1-[4-(benzyloxy)-3-fluorophenyl]ethanol (410mg) in THF (8mL) and water (2mL) was treated with PPh₃ (410mg) and stirred for 1h prior to addition of further with PPh₃ (220mg). After stirring for a further 4h the reaction mixture was concentrated in vacuo and the residue partitioned between EtOAc and water. The organic phase was washed three times with 5% NaHCO₃(aq) dried and concentrated *in* vacuo. The residue was purified by chromatography on silica gel, eluting with DCM, 1% MeOH in DCM, 2% MeOH in DCM, 5% MeOH containing 0.5% Et₃N in DCM, and finally 20% MeOH containing 1% Et₃N in DCM) to give *the title compound* (260mg). LCMS RT= 2.16 min.

15 iv) 4-[(1R)-2-Amino-1-hydroxyethyl]-2-fluorophenol

Palladium on carbon (10% Pd by weight, wet, 50mg) was flushed with nitrogen and treated with a solution of (1R)-2-amino-1-[4-(benzyloxy)-3-fluorophenyl]ethanol (500mg) in ethanol (25mL), EtOAc (25mL) and acetic acid (10mL). The reaction mixture was stirred under hydrogen for 5 h prior to flushing the reaction mixture with nitrogen and filtering to remove the catalyst and concentrating *in vacuo*. The residue was purified by chromatography (SCX, eluted with DCM, MeOH and DCM-MeOH-NH₃(aq) 100:10:1) to give *the title compound* (308mg). δ_H (400MHz, CD₃OD) 7.05 (1H, dd, J 2, 12Hz), 6.94 (1H, dd, J 2, 9Hz), 6.86 (1H, t, J 9Hz), 4.54 (1H, dd, J 5, 8Hz), 2.78 (1H, d, J 5Hz), 2.77 (1H, d, J 8Hz).

25

v) 3-{4-[(2R)-2-(3-Fluoro-4-hydroxyphenyl)-2-hydroxyethyl]amino}hexyl]oxy]butyl}benzenesulfonamide formate

A stirred solution of 4-[(1R)-2-amino-1-hydroxyethyl]-2-fluorophenol (45mg), diisopropylethylamine (0.06ml) and 3-{4-[(6-bromohexyl)oxy]butyl}benzenesulfonamide (86mg) in *N,N*-dimethylformamide (1ml) under nitrogen was heated to 50° for 18h. The mixture was cooled to 20°, the solvent evaporated *in vacuo* and the residue purified by mass-directed autopreparative HPLC to give the *title compound* (36mg). LCMS RT = 2.37min, ES +ve 483 (MH)⁺.

35 EXAMPLE 8

3-(4-{{[6-({2-Hydroxy-2-[5-hydroxy-6-(hydroxymethyl)pyridin-2-yl}ethyl)amino]hexyl}oxy}butyl)benzenesulfonamide formate

A stirred solution of 2-amino-1-(2-phenyl-4H-[1,3]dioxino[5,4-*b*]pyridin-6-yl)ethanol

(100mg) (EP220054A2), diisopropylethylamine (0.08ml) and 3-{4-[({6-

5 *bromohexyl)oxy]butyl}benzenesulfonamide (120mg) in *N,N*-dimethylformamide (2ml) under nitrogen was heated to 50° for 18h. The mixture was cooled to 20° and the solvent evaporated *in vacuo*. The residue was dissolved in acetic acid (4ml) and water (2ml) and was heated to 70° for 18h. The mixture was cooled to 20°, the solvent evaporated *in vacuo* and the residue purified by mass-directed autopreparative HPLC to give the *title**

10 *compound* (22mg). LCMS RT = 2.23min, ES +ve 496 (MH)⁺.

EXAMPLE 9

3-[4-{{6-[(2*R*)-2-Hydroxy-2-{4-hydroxy-3-

[(methylsulfonyl)amino]phenyl}ethyl)amino]hexyl}oxy}butyl]benzenesulfonamide formate

15

i) *N*-[2-Hydroxy-5-((1*R*)-1-hydroxy-2-{{(1*S*)-2-hydroxy-1-phenylethyl}amino}ethyl)phenyl]methanesulfonamide

A solution of *N*-[5-(bromoacetyl)-2-hydroxyphenyl]methanesulfonamide (*J. Med. Chem.*

1967, 10, 462-72) (1.15g) in dry DMF (30mL) was treated with diisopropylethylamine

20 (1.06mL) and (S)-phenylglycinol (474mg) and the reaction mixture stirred at room temperature for 4h. The reaction mixture was concentrated *in vacuo* and the residue re-suspended in methanol (50mL). The reaction mixture was cooled to 0°C and treated with CaCl₂ (1.27g). The reaction mixture was stirred at 0°C for 30 min prior to portionwise addition of NaBH₄ (218mg) ensuring that the temperature did not rise above 10°C . After 25 complete addition the reaction mixture was allowed to warm to room temperature and stirred for a further 74h. The reaction mixture was concentrated *in vacuo* and the residue partitioned between EtOAc and water. The organic phase was dried and concentrated *in vacuo*. The mixture was purified by chromatography (SPE, gradient from DCM to DCM-MeOH-NH₃(aq) 100:10:1) afforded the *title compound* (85mg). LCMS RT= 2.48min

30

ii) *N*-{5-[(1*R*)-2-Amino-1-hydroxyethyl]-2-hydroxyphenyl}methanesulfonamide

Palladium hydroxide (40mg, 50% water) was flushed with nitrogen and treated with a

35 solution of *N*-[2-hydroxy-5-((1*R*)-1-hydroxy-2-{{(1*S*)-2-hydroxy-1-phenylethyl}amino}ethyl)phenyl]methanesulfonamide (400mg) in methanol (80mL) and acetic acid (0.5mL). The reaction mixture was stirred under hydrogen for 16 h prior to

flushing the reaction mixture with nitrogen and filtering to remove the catalyst and concentrating *in vacuo*. The residue was purified by chromatography (OASIS, eluted with water, 5% MeOH in water 50% MeOH in water and MeOH) to give *the title compound* (182mg). δ_H (400MHz, CD₃OD) 7.38 (1H, d, *J* 2Hz), 7.12 (1H, dd, *J* 2, 8Hz), 6.90 (1H, d, *J* 8Hz), 4.78 (1H, dd, *J* 2, 10Hz), 3.08 (1H, dd, *J* 2, 15Hz), 2.98 (1H, bd, *J* 10Hz), 2.93 (3H, s).

iii) 3-[4-{[6-[(2R)-2-Hydroxy-2-{4-hydroxy-3-

[(methylsulfonyl)amino]phenyl}ethyl]amino]hexyl}oxy]butyl]benzenesulfonamide formate

10 A stirred solution of 1-{5-[(1*R*)-2-amino-1-hydroxyethyl]-2-hydroxyphenyl}methanesulfonamide (65mg), diisopropylethylamine (0.06ml) and 3-{4-[(6-bromohexyl)oxy]butyl}benzenesulfonamide (86mg) in *N,N*-dimethylformamide (1ml) under nitrogen was heated to 50° for 48h. The mixture was cooled to 20°, the solvent evaporated *in vacuo* and the residue purified by mass-directed autoreparative HPLC to give the *title compound* (12mg). LCMS RT = 2.31min ES +ve 558 (MH)⁺.

EXAMPLE 10

3-[3-{[7-{[(2R)-2-(3-Fluoro-4-hydroxyphenyl)-2-

hydroxyethyl]amino]heptyl}oxy]propyl]benzenesulfonamide formate

20 Prepared using methods similar to those described in Example 7.
LCMS RT = 2.37 min, ES +ve 483 (MH)⁺.

EXAMPLE 11

3-(3-{[7-{[2-Hydroxy-2-[5-hydroxy-6-(hydroxymethyl)pyridin-2-

y]ethyl]amino]heptyl}oxy]propyl]benzenesulfonamide formate

25 Prepared using methods similar to those described in Example 8.
LCMS RT = 2.22 min, ES +ve 496 (MH)⁺.

EXAMPLE 12

3-[3-{[7-{[(2R)-2-Hydroxy-2-{4-hydroxy-3-

[(methylsulfonyl)amino]phenyl}ethyl]amino]heptyl}oxy]propyl]benzenesulfonamide formate

30 Prepared using methods similar to those described in Example 9.
LCMS RT = 2.33 min, ES +ve 558 (MH)⁺.

EXAMPLE 13

3-[3-[(2R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino]heptyl]oxy]propyl}benzenesulfonamide acetate

- 5 i) 5-[(1R)-2-(Benzylamino)-1-hydroxyethyl]-8-(benzyloxy)quinolin-2(1H)-one
8-(Benzyl oxy)-5-[(2R)-oxiran-2-yl]quinolin-2(1H)-one (0.102g) (WO 9525104), was dissolved in benzylamine (0.5ml) and heated in a microwave oven for 15min at 150°C. Excess benzylamine was removed by evaporation on a rotary evaporator and the residue was purified on a silica SPE cartridge using methanol-dichloromethane-0.880 ammonia mixtures, to give *the title compound* (106mg) LCMS RT=2.30min
- 10 ii) 3-(3-[(7-(Benzyl{(2R)-2-[8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-hydroxyethyl}amino)heptyl]oxy}propyl)benzenesulfonamide
5-[(1R)-2-(Benzylamino)-1-hydroxyethyl]-8-(benzyloxy)quinolin-2(1H)-one (48mg) was dissolved in acetonitrile (2ml). N, N-diisopropylethylamine (0.042ml), and 3-{3-[(7-bromoheptyl)oxy]propyl}benzenesulfonamide (43mg) were added to the solution, which was heated at reflux for 72h under nitrogen. The mixture was diluted with water and extracted with ethyl acetate. The organic extracts were combined, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified on a silica SPE cartridge eluting with ethyl acetate- cyclohexane mixtures to give *the title compound* (36mg). LCMS RT=2.76min
- 15 iii) 3-{3-[(7-[(2R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino)heptyl]oxy}propyl}benzenesulfonamide acetate
A solution of 3-(3-[(7-(benzyl{(2R)-2-[8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-hydroxyethyl}amino)heptyl]oxy}propyl)benzenesulfonamide (36mg) in ethanol (10ml) with ethyl acetate (2ml) and glacial acetic acid (1ml) was hydrogenated using 10% palladium on carbon (50% water by weight, 10 mg) and 20% palladium hydroxide on carbon (10mg) for 19 h. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was purified on an aminopropyl SPE cartridge (2g), eluting with methanol-dichloromethane mixtures. Evaporation of the appropriate fractions with glacial acetic acid gave *the title compound* (15mg). LCMS RT= 2.26min ES+ve m/z 532 (MH^+)

BIOLOGICAL ACTIVITY

The potencies of the aforementioned compounds were determined using frog melanophores transfected with the human beta 2 adrenoreceptor. The cells were

5 incubated with melatonin to induce pigment aggregation. Pigment dispersal was induced by compounds acting on the human beta 2 adrenoreceptor. The beta 2 agonist activity of test compounds was assessed by their ability to induce a change in light transmittance across a melanophore monolayer (a consequence of pigment dispersal). At the human beta 2 adrenoreceptor, compounds of examples 1-13 had IC₅₀ values below 1 µM.

10

Potency at other beta adrenoreceptor subtypes was determined using chinese hamster ovary cells transfected with either the human beta 1 adrenoreceptor or the human beta 3 adrenoreceptor. Agonist activity was assessed by measuring changes in intracellular cyclic AMP.

15

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include,

20 by way of example and without limitation, the following claims:

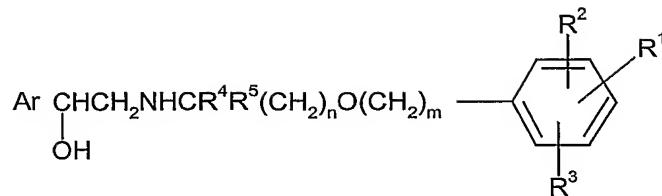
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CLAIMS

1. A compound of formula (I)

5



(I)

or a salt, solvate, or physiologically functional derivative thereof, wherein:

10 n is an integer of from 2 to 8;

m is an integer of from 3 to 11, with the proviso that the sum of n + m is from 5 to 19;

R¹ is hydrogen or -XSO₂NR⁶R⁷;

15 wherein X is -(CH₂)_p- or C₂₋₆ alkenylene;

p is an integer from 0 to 6;

20 R⁶ and R⁷ are independently selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, CONR⁸R⁹, phenyl and phenyl(C₁₋₄alkyl)-,

or R⁶ and R⁷, together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered nitrogen – containing ring;

25 and R⁶ and R⁷ are each independently optionally substituted by 1 or 2 groups independently selected from halo, C₁₋₆alkyl, C₁₋₆alkoxy, hydroxy-substituted C₁₋₆alkoxy, C₁₋₆haloalkyl, CO₂R⁸, SO₂R⁸R⁹, -CONR⁸R⁹, -NR⁸C(O)R⁹ or a 5-, 6- or 7- membered heterocyclic ring;

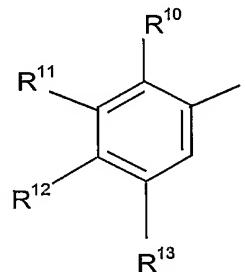
R^8 and R^9 are independently selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl and phenyl(C_{1-6} alkyl)-;

R^2 and R^3 are independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, halo, phenyl
5 and C_{1-6} haloalkyl;

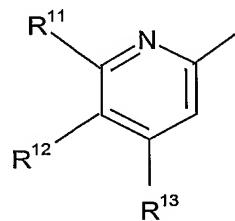
R^4 and R^5 are independently selected from hydrogen and C_{1-4} alkyl with the proviso that the total number of carbon atoms in R^4 and R^5 is not more than 4,

10 and

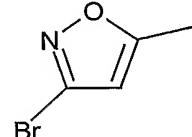
Ar is a group selected from



(a)

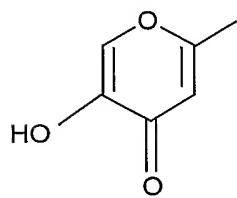


(b)



(c)

and



(d)

15

wherein R^{11} represents hydrogen, halogen, $-(CH_2)_qOR^{14}$, $-NR^{14}C(O)R^{15}$, $-NR^{14}SO_2R^{15}$, $-SO_2NR^{14}R^{15}$, $-NR^{14}R^{15}$, $-OC(O)R^{16}$ or $OC(O)NR^{14}R^{15}$,

and R¹⁰ represents hydrogen, halogen or C₁₋₄ alkyl;

or R¹¹ represents -NHR¹⁷ and R¹⁰ and -NHR¹⁷ together form a 5- or 6- membered heterocyclic ring;

5

R¹² represents hydrogen, halogen, -OR¹⁴ or -NR¹⁴R¹⁵; -OC(O)R¹⁶ or -OC(O)NR¹⁴R¹⁵;

R¹³ represents hydrogen, halogen, haloC₁₋₄ alkyl, -OR¹⁴ or -NR¹⁴R¹⁵;

10 R¹⁴ and R¹⁵ each independently represents hydrogen or C₁₋₄ alkyl, or in the groups -NR¹⁴R¹⁵, -SO₂NR¹⁴R¹⁵ and -OC(O)NR¹⁴R¹⁵, R¹⁴ and R¹⁵ independently represent hydrogen or C₁₋₄ alkyl or together with the nitrogen atom to which they are attached form a 5-, 6- or 7- membered nitrogen-containing ring,

15 R¹⁶ represents an aryl (eg phenyl or naphthyl) group which may be unsubstituted or substituted by one or more substituents selected from halogen, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy or halo C₁₋₄ alkyl; and

q is zero or an integer from 1 to 4;

20

provided that when R¹ is hydrogen

Ar is not a group (a) wherein;

R¹¹ is -(CH₂)_qOR¹⁴, q is zero or 1 and R¹² is OR¹⁴,

or R¹¹ is -(CH₂)_qOR¹⁴, q is zero and R¹³ is OR¹⁴,

25 or R¹¹ is -NR¹⁴SO₂R¹⁵ or NR¹⁴COR¹⁵ and R¹² is OR¹⁴,

or R¹¹ and R¹³ both represent halogen and R¹² is NR¹⁴R¹⁵;

Ar is not a group (b) wherein R¹¹ is -(CH₂)_qOR¹⁴ and R¹² is OR¹⁴;

Ar is not a group (c),

and when R¹ is XSO₂NR⁶R⁷, Ar is not a group (a) wherein

30 R¹¹ is (CH₂)_qOR¹⁴ or NR¹⁴COR¹⁵, and R¹² is OR¹⁴.

2. A compound of formula (I) according to claim 1 wherein, in the group Ar, R¹¹ represents halogen, -(CH₂)_qOR¹⁴, -NR¹⁴C(O)R¹⁵, -NR¹⁴SO₂R¹⁵, -SO₂NR¹⁴R¹⁵, -NR¹⁴R¹⁵, -OC(O)R¹⁶ or OC(O)NR¹⁴R¹⁵,

35

and R¹⁰ represents hydrogen,

or R¹¹ represents -NHR¹⁷ and R¹⁰ and -NHR¹⁷ together form a 5- or 6- membered heterocyclic ring;

5

and

R¹³ represents hydrogen, halogen, haloC₁₋₄ alkyl, -OR¹⁴, or -NR¹⁴R¹⁵;

10 and all other substituents are as defined in claim 1.

3. A compound of formula (I) according to claim 1 or claim 2 wherein the group R¹ is attached to the meta-position relative to the -O-(CH₂)_m link.

15 4. A compound of formula (I) according to any of claims 1 to 3 wherein R¹ represents SO₂NR⁶R⁷ wherein R⁶ and R⁷ are independently selected from hydrogen and C₁₋₆alkyl.

5. A compound of formula (I) according to any of claims 1 to 4 wherein R⁴ and R⁵ are independently selected from hydrogen and methyl.

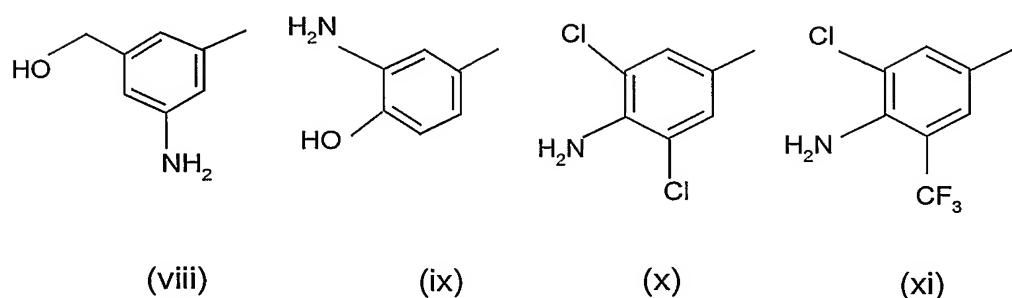
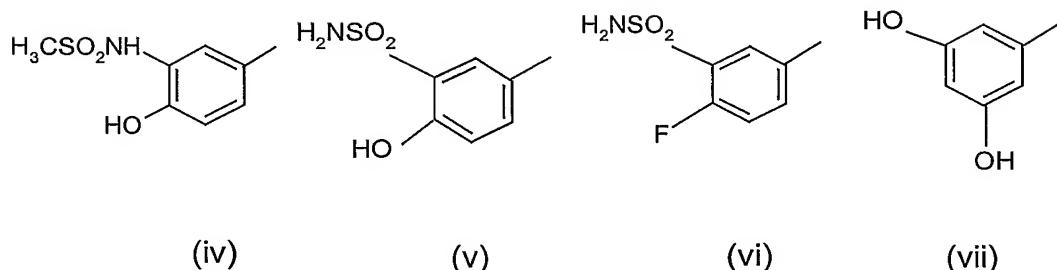
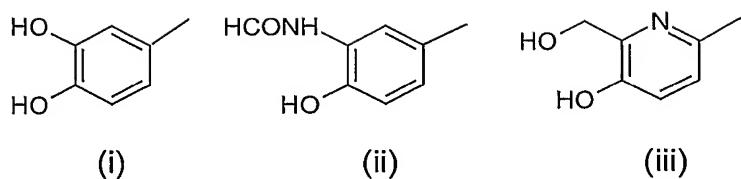
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6. A compound of formula (I) according to any of claims 1 to 5 wherein R² and R³ each represent hydrogen.

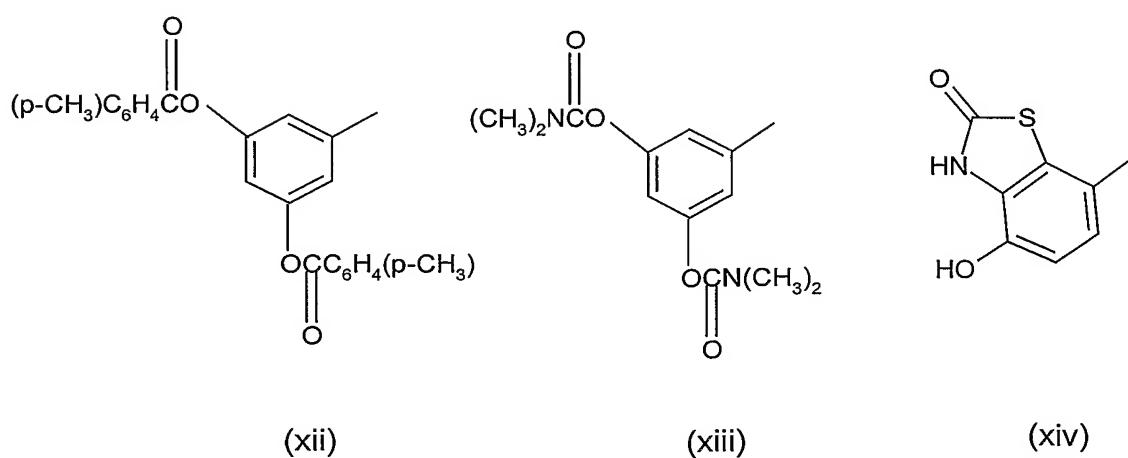
25 7. A compound of formula (I) according to any of claims 1 to 6 wherein n is 5 or 6 and m is 3 or 4 such that m + n is 8, 9 or 10.

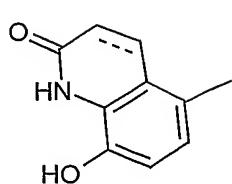
8. A compound of formula (I) according to any of claims 1 to 7 wherein Ar represents a group selected from:

30

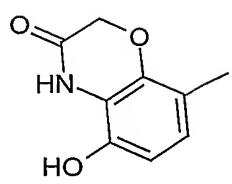


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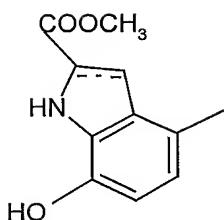
(xv)



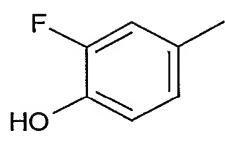
(xvi)



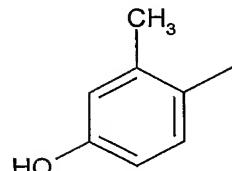
(xvii)



(xviii)



(xix)



(xx)

5 9. A compound of formula (I) according to any of claims 1 to 8 wherein R¹ is hydrogen and Ar is selected from a group of structure (ii), (v), (vi), (viii), (ix), (xi), (xii), (xiii), (xiv), (xv), (xvi), (xvii) and (xviii).

10 10. A compound of formula (I) according to any of claims 1 to 8 wherein R¹ is XSO₂NR⁶R⁷ and Ar is selected from a group of structure (iii), (iv), (xiv), (xv), (xvi) and (xix)

11. A compound of formula (I) selected from:
 8-Hydroxy-5-((1*R*)-1-hydroxy-2-[(6-(4-phenylbutoxy)hexyl]amino}ethyl)quinolin-2(1*H*)-one;
 3-{4-[(2*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-
 15 yl)ethyl]amino}hexyl]oxy]butyl}benzenesulfonamide;
 5-Hydroxy-8-(1-hydroxy-2-[(6-(4-phenylbutoxy)hexyl]amino}ethyl)-2*H*-1,4-benzoxazin-
 3(4*H*)-one;
 3-{4-[(6-{[2-hydroxy-2-(5-hydroxy-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-8-
 yl)ethyl]amino}hexyl]oxy]butyl}benzenesulfonamide;

4-Hydroxy-7-((1*R*)-1-hydroxy-2-{{6-(4-phenylbutoxy)hexyl}amino}ethyl)-1,3-benzothiazol-2(3*H*)-one;

4-Hydroxy-7-(1-hydroxy-2-{{6-(4-phenylbutoxy)hexyl}amino}ethyl)-1,3-benzothiazol-2(3*H*)-one;

- 5 3-{4-[(6-[(2*R*)-2-(3-Fluoro-4-hydroxyphenyl)-2-hydroxyethyl]amino}hexyl]oxy]butyl}benzenesulfonamide;
3-(4-{{6-({2-Hydroxy-2-[5-hydroxy-6-(hydroxymethyl)pyridin-2-yl]ethyl}amino)hexyl]oxy}butyl)benzenesulfonamide;
3-[4-{{6-[(2*R*)-2-Hydroxy-2-{4-hydroxy-3-
- 10 [(methylsulfonyl)amino]phenyl}ethyl]amino}hexyl]oxy]butyl}benzenesulfonamide;
3-{3-[(7-[(2*R*)-2-(3-Fluoro-4-hydroxyphenyl)-2-hydroxyethyl]amino)heptyl]oxy}propyl}benzenesulfonamide;
3-(3-{{7-({2-Hydroxy-2-[5-hydroxy-6-(hydroxymethyl)pyridin-2-yl]ethyl}amino)heptyl]oxy}propyl)benzenesulfonamide;
- 15 3-[3-{{7-[(2*R*)-2-Hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)amino]phenyl}ethyl]amino}heptyl]oxy}propyl}benzenesulfonamide;
3-{3-[(7-[(2*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino)heptyl]oxy}propyl}benzenesulfonamide;
3-(3-{{7-[(2*R*)-2-[3-(Formylamino)-4-hydroxyphenyl]-2-hydroxyethyl}amino)heptyl]oxy}propyl)benzenesulfonamide;
- 20

or a salt, solvate or physiologically functional derivative thereof.

12. A method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I) according to any of claims 1 to 11, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

30 13. A compound of formula (I), according to any of claims 1 to 11, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy.

35 14. A pharmaceutical formulation comprising a compound of formula (I), according to any of claims 1 to 11, or a pharmaceutically acceptable salt, solvate, or physiologically

functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

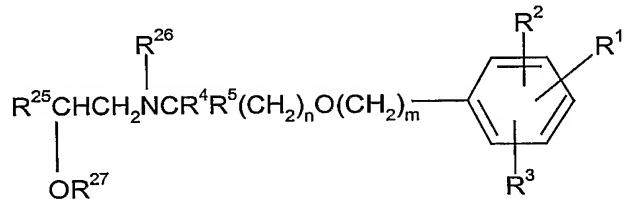
15. The use of a compound of formula (I), according to any of claims 1 to 11, or a

5 pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2 -adrenoreceptor agonist is indicated.

16. A process for the preparation of a compound of formula (I), according to any of

10 claims 1 to 11, or a salt, solvate, or physiologically functional derivative thereof, which comprises:

(a) deprotection of a protected intermediate of formula (II):



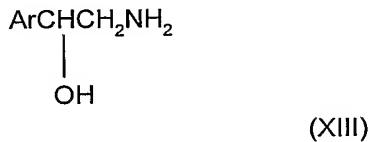
(II)

15

or a salt or solvate thereof, wherein R¹, R², R³, R⁴, R⁵, m and n are as defined for the compounds of formula (I) R²⁵ represents an optionally protected form of Ar, and R²⁶ and R²⁷ each independently represent either hydrogen or a protecting group, provided that the compound of formula (II) contains at least one protecting group;

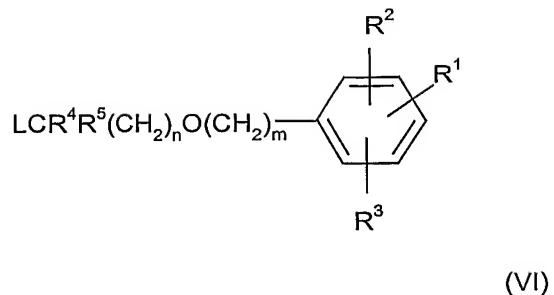
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(b) reacting a compound of formula (XIII):



(XIII)

Wherein Ar is as defined above with a compound of formula (VI):



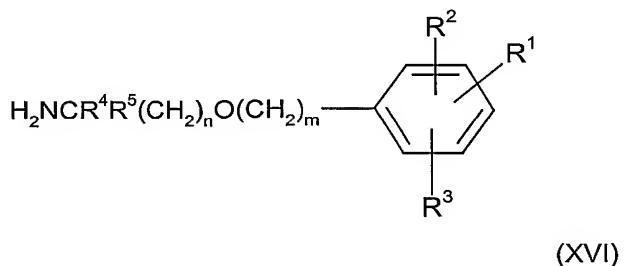
Wherein L is a leaving group such as halo (typically chloro, bromo or iodo) or a sulphonate (typically methanesulphonate) and R¹, R², R³, R⁴, R⁵, n and m are as defined
5 for compounds of formula (I).

(c) reacting a compound of formula (XV):



10

wherein L is a leaving group as hereinbefore defined, with an amine of formula (XVI):

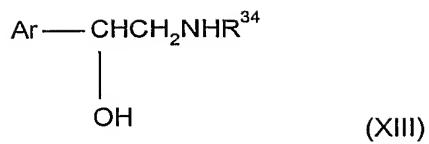


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wherein R¹, R², R³, R⁴, R⁵, n and m are as defined for formula (I); and

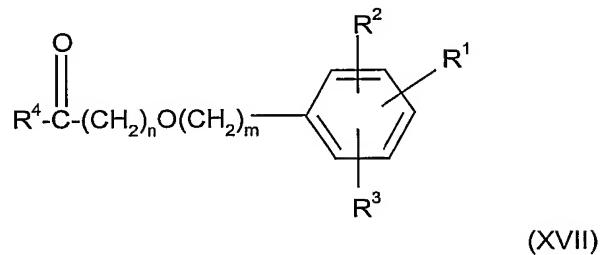
(d) (i) reacting a compound of formula (XIII):

20



Wherein Ar is as hereinbefore defined and R³⁴ is a chiral auxiliary group,

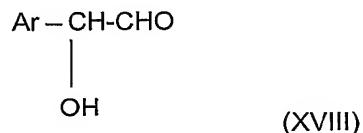
5 with a compound of formula (XVII):



wherein R¹, R², R³, R⁴, n and m are as hereinbefore defined;
followed where necessary by removal of said chiral auxiliary group R³⁴;

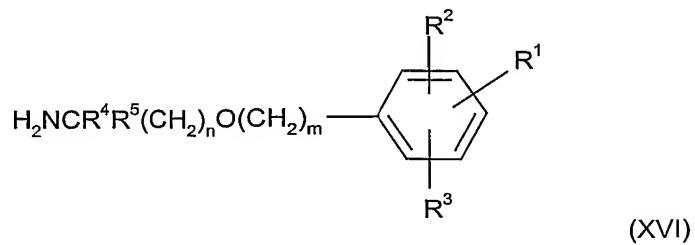
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or (ii) reacting a compound of formula (XVIII):



wherein Ar is as hereinbefore defined; with an amine of formula (XVI):

15



as hereinbefore defined,

5 under conditions suitable to effect reductive amination,

followed by the following steps in any order:

- (i) optional removal of any protecting groups;
- 10 (ii) optional separation of an enantiomer from a mixture of enantiomers;
- (iii) optional conversion of the product to a corresponding salt, solvate,
- (iv) optional conversion of a group R¹, R² and/or R³ to another group R¹, R² and/or R³,

or physiologically functional derivative thereof.

15

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(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
26 February 2004 (26.02.2004)

PCT

(10) International Publication Number
WO 2004/016578 A3

(51) International Patent Classification⁷: **C07C 217/10**,
311/29, 213/00, 303/40, C07D 215/26, 213/65, 265/36,
277/68

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Road, Stevenage, Hertfordshire SG1 2NY (GB).

(21) International Application Number:
PCT/EP2003/008264

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West Road, Brentford, Middlesex TW8 9GS (GB).

(22) International Filing Date: 24 July 2003 (24.07.2003)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC,
SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,
UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English

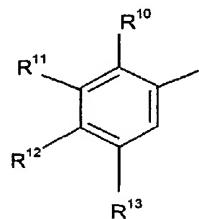
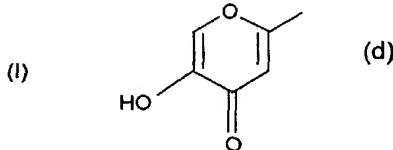
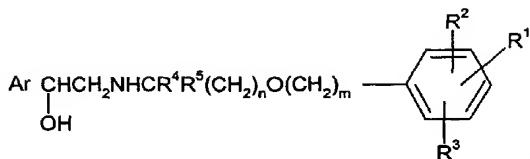
(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(26) Publication Language: English

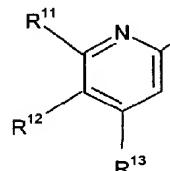
Published:
— with international search report

[Continued on next page]

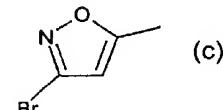
(54) Title: ARYLETHANOLAMINE BETA2-ADRENORECEPTOR AGONIST COMPOUNDS



(a)



(b)



(c)

WO 2004/016578 A3

(57) Abstract: The present invention concerns compounds of formula (I) and salts, solvates, and physiologically functional derivatives thereof, wherein: R¹ is hydrogen or -XSO₂NR⁶R⁷; R² and R³ are independently selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo, phenyl and C₁₋₆ haloalkyl and Ar is a group selected from and. Processes for preparing said compounds and pharmaceutical formulations containing them are also described. Compounds of formula (I) are useful in the treatment of respiratory diseases



— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(88) Date of publication of the international search report:

10 June 2004

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08264

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	C07C217/10	C07C311/29	C07C213/00	C07C303/40	C07D215/26
	C07D213/65	C07D265/36	C07D277/68		

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95/19336 A (IOVIS BIOMEDICAL AND PHARMACEUTICAL; BRON JAN (NL); STERK GEERT JAN (NL);) 20 July 1995 (1995-07-20) claims 1,5-8; examples 1,5-7,9,16 page 15, paragraph 1 - page 16, paragraph 2 -----	1,3,5-7, 12-16
X	EP 0 220 054 A (GLAXO GROUP LTD) 29 April 1987 (1987-04-29) claims 1-3,9,10; examples 16,25 page 4, line 62 - page 5, line 6 -----	1-3,5-8, 12-16
X	EP 0 162 576 A (GLAXO GROUP LTD) 27 November 1985 (1985-11-27) cited in the application claims 1,8,9 page 5, paragraph 3 - page 6, paragraph 3 -----	1,2,5,8, 12-16
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

2 April 2004

Date of mailing of the international search report

21.04.2004

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Authorized officer

Krische, D

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08264

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 35 24 990 A (GLAXO GROUP LTD) 23 January 1986 (1986-01-23) cited in the application claims 1,15,16; examples 1-13 page 15, line 1 - line 29 page 22, line 25 - line 35 -----	1,12-16
A	GB 2 140 800 A (GLAXO GROUP LTD) 5 December 1984 (1984-12-05) cited in the application claims 1-11; examples 2-4,6-10 page 2, line 62 - page 3, line 15 -----	1,12-16
A	GB 2 230 523 A (GLAXO GROUP LTD) 24 October 1990 (1990-10-24) cited in the application claims 1-6; example 1 page 3, paragraph 2 - paragraph 4 page 6, paragraph 2 - page 8, paragraph 3 -----	1,12-16
A	DE 40 28 398 A (THOMAE GMBH DR K) 12 March 1992 (1992-03-12) claims 1,7,13 -----	16

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 12 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

**As a result of the prior review under R. 40.2(e) PCT,
part additional fees are to be refunded.**

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 12 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

Continuation of Box I.2

Claims Nos.: -

Present claims 1-16 relate to compounds of formula (I), salts, solvates or "physiologically functional derivatives" thereof. These "derivatives" are defined by reference to a desirable property, namely that they are "physiologically functional".

The claims cover all compounds having this property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of formula (I), salts, solvates and as "physiologically functional derivatives" esters thereof.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1,3-7,12-15 in part, 2,8-11

Compounds of formula (I) comprising groups Ar a) or b)
useful as beta2-adrenoreceptor agonists and methods and
formulations using these compounds.

2. claims: 1,3-7,12-15 in part

Compounds of formula (I) comprising group Ar c) useful as
beta2-adrenoreceptor agonists and methods and formulations
using these compounds.

3. claims: 1,3-7,12-15 in part

Compounds of formula (I) comprising group Ar d) useful as
beta2-adrenoreceptor agonists and methods and formulations
using these compounds.

4. claim: 16

Alternative processes for the preparation of compounds of
formula (I).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/08264

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 9519336	A	20-07-1995	AU 1533495 A WO 9519336 A1	01-08-1995 20-07-1995
EP 0220054	A	29-04-1987	CN 1048040 A EP 0220054 A2 JP 62174041 A US 4908386 A	26-12-1990 29-04-1987 30-07-1987 13-03-1990
EP 0162576	A	27-11-1985	AT 44955 T AU 581887 B2 AU 4134685 A DE 3571808 D1 DK 173685 A EP 0162576 A1 JP 60248650 A US 4853381 A ZA 8502853 A GB 2160863 A IL 75485 A NZ 212367 A PH 24383 A	15-08-1989 09-03-1989 24-10-1985 31-08-1989 18-10-1985 27-11-1985 09-12-1985 01-08-1989 29-01-1986 02-01-1986 31-10-1988 26-04-1989 13-06-1990
DE 3524990	A	23-01-1986	AU 582369 B2 AU 4486085 A BE 902876 A1 CH 665632 A5 DE 3524990 A1 DK 319885 A ES 8609216 A1 ES 8707925 A1 FI 852755 A FR 2567510 A1 GB 2162842 A ,B GR 851733 A1 HU 43556 A2 IL 75794 A IT 1182061 B JP 61050950 A LU 86002 A1 NL 8502012 A NO 852809 A NZ 212726 A PH 22666 A PT 80806 A ,B SE 8503466 A ZA 8505297 A ZA 8600193 A AT 39350 T CN 86102681 A ,B DE 3566885 D1 DK 13186 A EP 0178919 A2 FI 860107 A ,B, JP 1785301 C JP 4074345 B JP 61148150 A PT 81819 A ,B US 4853382 A	23-03-1989 16-01-1986 13-01-1986 31-05-1988 23-01-1986 14-01-1986 16-12-1986 16-11-1987 14-01-1986 17-01-1986 12-02-1986 26-11-1985 30-11-1987 31-01-1989 30-09-1987 13-03-1986 04-08-1986 03-02-1986 14-01-1986 24-02-1989 14-11-1988 01-08-1985 14-01-1986 30-04-1986 29-04-1987 15-01-1989 28-10-1987 26-01-1989 11-07-1987 23-04-1986 11-07-1987 31-08-1993 26-11-1992 05-07-1986 01-02-1986 01-08-1989

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/EP 03/08264

Patent document cited in search report	Publication date		Patent family member(s)	Publication date	
DE 3524990	A	US	4730008 A	08-03-1988	
GB 2140800	A	05-12-1984	AT 390611 B AT 129184 A AU 573212 B2 AU 2706484 A BE 899448 A1 BE 900835 A4 BG 61490 B2 CA 1335999 C CA 1336004 C CH 661497 A5 CH 667084 A5 CZ 9104028 A3 CY 1482 A CZ 285602 B6 DE 3414752 A1 DE 3448338 C2 DE 3448452 C2 DK 158092 A DK 201784 A ES 8505641 A1 ES 8609209 A1 FI 841548 A ,B, FR 2545482 A1 GB 2176476 A ,B GR 79925 A1 HK 36889 A HU 200160 B IE 57237 B1 IL 71569 A IT 1199112 B JP 1862136 C JP 5069817 B JP 63264443 A JP 1643826 C JP 3000858 B JP 59199659 A JP 2001385 C JP 6087800 A JP 7029997 B KE 3864 A KR 9204186 B1 LU 85329 A1 LU 88265 A9 MX 9203226 A1 NL 8401258 A ,B, NO 841568 A ,B, NZ 207885 A NZ 221999 A PH 21574 A PT 78443 A ,B	11-06-1990 15-11-1989 02-06-1988 25-10-1984 18-10-1984 17-04-1985 30-09-1997 20-06-1995 20-06-1995 31-07-1987 15-09-1988 12-05-1993 08-12-1989 15-09-1999 18-10-1984 19-05-1993 05-01-1994 30-12-1992 19-10-1984 01-10-1985 16-12-1986 19-10-1984 09-11-1984 31-12-1986 31-10-1984 12-05-1989 28-04-1990 17-06-1992 30-10-1987 30-12-1988 08-08-1994 01-10-1993 01-11-1988 28-02-1992 09-01-1991 12-11-1984 20-12-1995 29-03-1994 05-04-1995 19-05-1989 30-05-1992 04-06-1985 03-02-1994 01-07-1992 16-11-1984 19-10-1984 29-11-1988 29-11-1988 11-12-1987 01-05-1984	11-06-1990 15-11-1989 02-06-1988 25-10-1984 18-10-1984 17-04-1985 30-09-1997 20-06-1995 20-06-1995 31-07-1987 15-09-1988 12-05-1993 08-12-1989 15-09-1999 18-10-1984 19-05-1993 05-01-1994 30-12-1992 19-10-1984 01-10-1985 16-12-1986 19-10-1984 09-11-1984 31-12-1986 31-10-1984 12-05-1989 28-04-1990 17-06-1992 30-10-1987 30-12-1988 08-08-1994 01-10-1993 01-11-1988 28-02-1992 09-01-1991 12-11-1984 20-12-1995 29-03-1994 05-04-1995 19-05-1989 30-05-1992 04-06-1985 03-02-1994 01-07-1992 16-11-1984 19-10-1984 29-11-1988 29-11-1988 11-12-1987 01-05-1984
GB 2230523	A	24-10-1990	NONE		
DE 4028398	A	12-03-1992	DE 4028398 A1 AT 146774 T AU 8426191 A	12-03-1992 15-01-1997 30-03-1992	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/08264

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
DE 4028398	A		CA 2073042 A1	08-03-1992
			DE 59108433 D1	06-02-1997
			DK 500853 T3	07-04-1997
			WO 9204316 A1	19-03-1992
			EP 0500853 A1	02-09-1992
			ES 2097815 T3	16-04-1997
			GR 3022735 T3	30-06-1997
			IE 913136 A1	11-03-1992
			JP 5502455 T	28-04-1993
			JP 3164819 B2	14-05-2001
			NZ 239700 A	27-04-1995
			PT 98884 A ,B	31-07-1992
			US 5393774 A	28-02-1995
			ZA 9107086 A	08-03-1993

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
26 February 2004 (26.02.2004)

PCT

(10) International Publication Number
WO 2004/016578 A3

(51) International Patent Classification⁷: **C07C 217/10**,
311/29, 213/00, 303/40, C07D 215/26, 213/65, 265/36,
277/68

Duncan, Stuart [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).
LOOKER, Brian, Edgar [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

(21) International Application Number:
PCT/EP2003/008264

(74) Agent: FLORENCE, Julia, Anne; GlaxoSmithKline, Corporate Intellectual Property (CN925.1), 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(22) International Filing Date: 24 July 2003 (24.07.2003)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,

(26) Publication Language: English

(30) Priority Data:
0217225.2 25 July 2002 (25.07.2002) GB

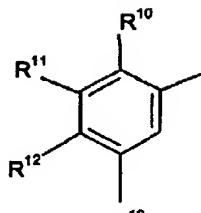
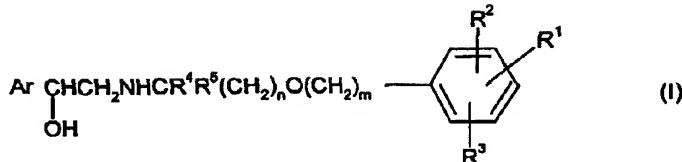
[Continued on next page]

(71) Applicant (for all designated States except US): **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

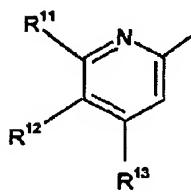
(72) Inventors; and

(75) Inventors/Applicants (for US only): **BIGGADIKE, Keith** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **COE, Diane, Mary** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **HOLMES,**

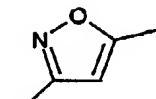
(54) Title: ARYLETHANOLAMINE BETA2-ADRENORECEPTOR AGONIST COMPOUNDS



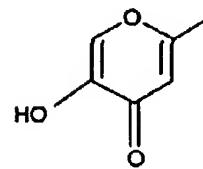
(a)



(b)



(c)



(d)

WO 2004/016578 A3

(57) Abstract: The present invention concerns compounds of formula (I) and salts, solvates, and physiologically functional derivatives thereof, wherein: R¹ is hydrogen or -XSO₂NR⁶R⁷; R² and R³ are independently selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo, phenyl and C₁₋₆ haloalkyl and Ar is a group selected from and. Processes for preparing said compounds and pharmaceutical formulations containing them are also described. Compounds of formula (I) are useful in the treatment of respiratory diseases



SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(48) Date of publication of this corrected version:

17 February 2005

Published:

— *with international search report*

(15) Information about Correction:

see PCT Gazette No. 07/2005 of 17 February 2005, Section II

(88) Date of publication of the international search report:

10 June 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.